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# Interactions of sodium ethacrynate in intravenous admixture with selected cardiovascular and psychotherapeutic agents

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# INTERACTIONS OF SODIUM ETHACRYNATE IN INTRAVENOUS ADMIXTURE WITH SELECTED CARDIOVASCULAR AND PSYCHOTHERAPEUTIC AGENTS

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by

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P.N.C.

University of the Pacific

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# I. INTRODUCTION

The possibility of drug incompatibilities is a matter of serious concern when administering two or more therapeutic agents. This is especially true in the case of parenteral administration when one must be aware not only of therapeutic interactions but also chemical and physical reactions that might occur.

In order to avoid incompatibilities, drug manufacturers have suggested that parenteral solutions be used immediately after reconstitution and that admixtures of parenteral products not be administered wherever possible (1,2). Physicians have also stressed the importance in avoiding multiple drug therapy (3,4). In spite of these suggestions, the practice of multiple drug therapy is prevalent.

Because of this, there has been an increase in awareness of the number of drug admixtures administered in the hospital. At the University of Michigan Hospital over two thirds of the intravenous fluids administered contained two or more therapeutic agents (5). Holysko and Ravin (6) report that 48% of the intravenous fluids contain one additive, 30% contain two additives, and 22% contain three or more additives. The survey taken by Patterson and Nordstrom (7) showed that 24% of the solutions administered intravenously contained two drugs, and that 16% of the intravenous solutions contained three or more additives.

The increased awareness of the problems in admixtures of parenterals has contributed to the increased use of centralized intravenous additive programs at various hospitals. The hospital pharmacist is now becoming more responsible for the preparation of intravenous admixtures (8). The need for additional information concerning potential interactions when admixtures of therapeutic agents for intra-

venous use are administered is evident. The lack of information includes, in addition to incompatibilities, areas of interest such as stability, sterility, and clinical effectiveness (8,9).

This report will discuss a method to detect potential chemical interactions. The drugs under investigation are sodium ethacrynate (Edecrin[a]) in combination with selected cardiovascular and psychotherapeutic agents when in admixture in normal saline solution. Possible therapeutic interactions and physical incompatibilities of these combinations will also be discussed.

## THERAPEUTIC INCOMPATIBILITIES

The first type of incompatibility to be considered is that which is concerned with therapeutic interactions. This refers to an interaction that may affect the safety or efficacy of the resulting admixture. Included in this category are drug-induced interactions such as potentiation, antagonism, inhibition, and the production of toxic side effects (10,11).

According to Dale (10) therapeutic interactions appear to occur more frequently with the more lipid soluble drugs. This may be due to the fact that lipid soluble drugs are more slowly excreted from the body. The altered response of the drug admixture may be the direct result of metabolism, transport, or renal clearance of the drug (4).

Therefore, in order to predict any potential therapeutic interaction correctly, one must be familiar with the mechanism of action of the drugs involved

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a - Merck, Sharp, Dohme, Div., Merck & Co., West Point, Pa.

in the admixture. A number of reports are available describing the mechanism of action of the potent diuretic, sodium ethacrynate. Published results show that the major site of action of sodium ethacrynate is the ascending limb of Henle's Loop (12-14). In addition, Hutcheon (14) states that sodium ethacrynate has a much shorter onset of action than the mercurials and the thiazide diuretics.

The effect of sodium ethacrynate upon the excretion of electrolytes is an important consideration in the discussion of this drug's mechanism of action. Most researchers agree that there is an increase in the excretion of sodium and chloride ions after administration of sodium ethacrynate (15-17). In the case of potassium ion excretion, the manufacturer's literature suggests the possibility of hypokalemia occurring (18). Published reports give conflicting results concerning the effect of sodium ethacrynate upon potassium levels in the body (13-18).

The administration of sodium ethacrynate in combination with the cardiovascular agents presents an interesting potential therapeutic interaction. This involves the administration of sodium ethacrynate with the digitalis drugs, digoxin and digitoxin. Various authors suggest that cardiac glycosides should not be administered with the potassium depleting diuretics (18-21). This suggestion seems to be a valid one since potassium plays a vital role in the mechanism of action of the cardiac glycosides (22). But in the case of sodium ethacrynate, it has not yet been definitely established if potassium depletion occurs as mentioned above. And in fact, various investigators have administered the cardiac glycosides prior to, and also concurrently with, sodium ethacrynate without harmful effects (23-28).

Therefore, the hospital pharmacist must be aware of the potential harmful effect of administering therapeutic agents in admixture. A knowledge of the mechanism of action, side effects, and fate in the body of admixtures of drugs is very important. The pharmacist, in preparing admixtures of parenteral products, should be able to predict and avoid any potential therapeutic interactions. A greater awareness of these problems on the part of the hospital pharmacist would be of great value. Nurses and physicians would then be free to perform their function in the hospital without having to cope with therapeutic incompatibilities.

## PHYSICAL INCOMPATIBILITIES

The second type of incompatibility is that which is concerned with physical interactions. These are considered to be those interactions that can be observed with the naked eye. Incompatibilities of this type manifest themselves as the formation of particulate matter such as a precipitate, flocculence, turbidity, cloudiness, color or odor change (29).

The study of intravenous admixtures and their potential physical incompatibilities is not new nor has there been a lack of research in this area of interest. As early as 1955 Bogash (30) published the results of his investigation of the compatibilities and incompatibilities of parenteral admixtures. His method of study consisted of preparing mixtures of various parenteral products in selected intravenous solutions. He then observed the solution for the appearance of particulate matter immediately after mixing and again four hours later. If no

particulate matter appeared within the four hour trial period, the mixture was considered to be compatible.

Kirkland and his wo-workers (31) determined the physical compatibilities of selected parenteral admixtures. The drug under consideration was added to 50 milliliter portions of various infusion fluids. The concentration used was that of the highest dosage level generally prescribed. Changes in color as well as haze or precipitate formation was noted immediately and at one, six and twenty-four hour periods. It should be noted that no attempt was made to determine the compatibilities of two drugs in an infusion fluid.

As is the case with several other compatibility studies, Riffkin's study centered primarily upon the parenteral products of a single manufacturer (32). Unfortunately the procedure used to determine compatibility was not published. He suggested that incompatibility is due to pH, viscosity, tonicity, particle size, oxidation, reduction, storage temperature, or exposure to light.

Misgen (33) determined the physical compatibilities of 34 drugs intended for intravenous use. In his work one milliliter of the initial drug was injected into a vial containing five milliliters of sterile distilled water. Into this solution was injected one milliliter of a solution of the combining drug and the resulting solution was checked immediately. A second check was made two hours later. If any particulate matter was observed, the combination was considered to be incompatible. No reference was made to the concentration of each drug used in this study.

Dunsworth and Kenna (34) performed a preliminary study on the physical incompatibilities of selected medications. A certain concentration of each

therapeutic agent was added to 100 milliliters of Dextrose Injection (5%). A total of 24 drugs was examined and several limitations of the procedure were outlined. These included such things as only one concentration of the drug was used and that chemical, bacteriological or physiological incompatibilities were not considered.

Patel and Phillips (35) used microscopic methods to determine the physical compatibilities of certain intravenous drug admixtures. Solutions of various drugs were prepared in selected infusion fluids. A drop of a solution was placed on a microscope slide and a drop of another solution was added. This mixture was examined under a microscope for the presence of particulate matter. If a mixture showed the development of a precipitate, then different dilutions of the same drug admixture were studied in the same manner.

As a result of the work undertaken in the area of physical incompatibilities, various compatibility charts have become available (36-38). These charts are based upon original research or are compilations of published studies on parenteral admixture incompatibilities. These charts usually list products frequently used in the hospital and indicate those mixtures which are compatible. While serving as a useful aid to the hospital pharmacist, these charts do have limitations and disadvantages. For example, any conclusion pertaining to admixture compatibility is based upon the detection of particulate matter. No claim is made concerning chemical or therapeutic incompatibility and the results are limited, therefore, to physical compatibility.

Another limitation in the use of the compatibility charts concerns the

concentrations used in the determination of the compatibility of the admixture. In most cases no mention is made of the amount of drug used in the infusion fluid under investigation. This may lead to errors in predicting and avoiding physical interactions, especially in those instances when the incompatibility may be dependent upon the concentrations of the reactants.

Because of the lack of uniformity in the methods that have been used to detect physical incompatibility, those guides which are merely compilations of the work of various investigators are actually accumulations of the results of admixture studies based upon different methods of detection. It is important to be familiar with the methods used to determine compatibility, especially if the methods do not simulate actual clinical practice. The validity of the results may be questioned if the methods bear little correlation to procedures used in medical treatment.

In comparing the various published compatibility charts, one can easily note inconsistencies. The cause for these inconsistencies can be attributed to a number of variables. One such important variable is the brand of parenteral product used in the study. Additives such as buffers and preservatives vary from manufacturer to manufacturer. While these additives are considered to be therapeutically inert, they may be the cause of incompatibility. For this reason a parenteral product manufactured by one company may be compatible in admixture, while the corresponding parenteral product manufactured by another company may not.

Another variable to be considered is the concentration of the drugs in

the infusion fluid. A reaction may or may not occur depending upon the concentration of the reactants. For this reason, one must be aware of the concentrations used in the various compatibility charts.

Different methods used to detect physical interactions introduce important inconsistencies in the published compatibility charts. Further, variations in the order of mixing and the period of storage must be considered when applying the findings of previous studies to prediction of compatibility in the clinical situation. Considering the fact that varying experimental methods have been used by different investigators, one can gauge the complexity of the problem.

## CHEMICAL INCOMPATIBILITIES

The third type of incompatibility manifests itself as a result of some type of chemical interaction. It has been defined as any reaction or interaction that does not produce a visible change in the resultant solution but that which will decrease the effectiveness of one or both of the additives (10). This interaction can be related to the acidic or basic characteristics of the drugs involved, or to oxidation, reduction, hydrolysis, or other forms of chemical reaction.

It has been suggested that the term chemical incompatibility is a misnomer (39), because both a physical and a chemical incompatibility must begin with a chemical reaction. A more meaningful term would be a "non visual" incompatibility. Additional terminology suggested has been "soluble" and "insoluble" incompatibility (40). These suggestions are based upon one major difference between the definition of physical and chemical incompatibility, which is the solubility of the end products of the reaction. Plein (41) agrees and further states

that chemical interactions are not visible because the by-products of the reaction are soluble.

Little published information is available on chemical incompatibility of intravenous admixtures. Perhaps, part of the reason for lack of information concerning this area of incompatibility is the difficulty in detecting a chemical reaction that does not produce a visible change in the system. As stated by Parker (1) methods of analysis must be devised in which decomposition can be detected, even in the presence of other drugs that might interfere.

Methods to detect chemical interactions have been based upon pH studies and stability studies to determine the loss of activity of the therapeutic agents. As defined by Schou (42) stability is that period of time when a preparation no longer fulfills the specifications of the Pharmacopeia or until the potency of the preparation has been reduced by more than ten per cent.

The stability of tetracycline was studied by Huang and his co-workers (43). They determined the stability of tetracycline in relation to pH and temperature. Biological tests and also change in absorbance at the wavelength of maximum absorbance of the drug were used to detect any loss in activity. This work was not concerned with any admixtures but did demonstrate a method to detect the loss in activity of tetracycline.

As heat greatly affects the stability of tetracycline, Garrett (44) attempted to detect the end products of tetracycline after heating its solution. To accomplish this determination, spectrophotometric analysis was employed.

His results were based upon a complete ultraviolet (U.V.) scan of tetracycline before and after heating. The shift in the U.V. absorption maxima of tetracycline after heating was consistent with the expected scan if the tetracycline was transformed in part to anhydrotetracycline.

Gallelli (45) determined the percentage potency of selected drugs in different parenteral solutions. A total of six drugs in two intravenous infusion fluids were studied. Three drugs were assayed spectrophotometrically and three were assayed microbiologically. The percentage potency was determined using the absorbance at a specific wavelength, and stability was determined over a twelve day period.

One of the earlier studies to detect loss of activity of therapeutic agents in admixture was performed by Dony-Crotteux (46). He studied the inactivation of antibiotics by vitamins. By the use of the growth curve method, he was able to determine the effect of various vitamins in solution with selected antibiotics.

Im and Latiolais (47) determined the physico-chemical incompatibilities of admixtures of penicillins and tetracyclines in Dextrose Injection, U.S.P. It was assumed that the incompatibility was due to the difference in pH of the drugs. The pH of the solutions were altered and degradation due to the acidic and basic character was detected spectrophotometrically. The mixtures were rated incompatible if a loss in absorbance occurred at the wavelength of maximum absorption for each drug.

Parker (1) presented an interim report of a chemical compatibility study. Involved were some common examples of incompatibilities which do not produce

a visual change in the mixtures. Eight parenteral products in various intravenous fluids were examined but no mention was made of the method of testing the solutions.

Edward (48) considered pH to be an important factor in the prediction of admixture instability. In that study, the pH change in an intravenous vehicle was determined after a drug or drugs were added. This information was then compared to the known pH stability range of each drug. The results of the comparison were used to predict the possible acid-base stability of the drugs in a vehicle.

Carlin and Perkins (49) discussed a method to predict potential chemical reactions. Drugs under consideration were the penicillins, the tetracyclines, B complex vitamins, hydrocortisone, and aminophylline. The influence of the acidic or basic character of the additives on their reactivity was emphasized. Using chemical incompatibility data, they were able to devise a method of estimating the reaction rates of certain additives. This method involved calculating the time required for ten per cent of the drug to react. Therefore, these authors calculated, the time necessary for the admixture to lose ten percent of its original potency.

Similar to the work of Carlin and Perkins, is the study of Webb (40). He attempted to predict a pH pattern for intravenous additives. His work was based upon the pH and the solubility of the drugs in admixture. The degree of solubility is dependent upon the pH of the infusion fluid and the concentration of the additives. By using an appropriate equation, one can predict the pH at which the free acid of a soluble organic compound may begin to precipitate.

Parker (39) suggested the use of the pH profile as a useful tool in assessing chemical interactions. The pH profile is a laboratory simulation of the effect of pH upon a specific drug. The purpose of this profile was to identify potential problem areas in order that they might be avoided. The profiles were determined by adjusting the pH of the solutions with acid or base to simulate the addition of acidic or basic drugs to the test solutions. In each study a ten per cent potency loss was considered significant.

It must be noted that one should use pH values with care in predicting possible incompatibilities. As will be discussed later, there are several variables that might affect the pH stability, and therefore cause changes in the pH values.

As can be noted from the above discussion, the available information concerning chemical incompatibilities of intravenous admixtures is of a limited nature. This lack of information may be attributed to the fact that methods of detecting chemical interactions are difficult and usually involve indirect methods of study. Any method that is used must include consideration of several variables. These variables include the concentration of the additives, the rate of the reaction, the effect of the infusion fluid, pH, and the similarity of the method to actual clinical practice.

The purpose of this author's work is to devise a new method of detecting physical and chemical interactions of intravenous admixtures. This method will include the use of procedures that will duplicate actual clinical practice. Close correlation with the hospital situation will provide results that can be easily applied to problems associated with a centralized intravenous additive program.

Concentrations normally employed in clinical practice will be evaluated. It is likely that any chemical changes after admixture will be reflected in an alteration of the U.V. spectrum for each drug. The use of each of the drugs of an admixture pair could serve as the reference standard for evaluating a change in the other compound. The results which follow appear to bear out the utility of this method.

## II. EXPERIMENTAL METHOD

In an attempt to detect physical and chemical interactions of intravenous admixtures, sodium ethacrynate in combination with selected cardiovascular and psychotherapeutic agents were investigated. Sodium ethacrynate was added to Sodium Chloride Injection, U.S.P.[a], and then mixed with each of the following parenteral products: Hydralazine Hydrochloride (Apresoline[b]), Tolazoline Hydrochloride (Priscoline[b]), Reserpine (Serpasil[b]), Prochlorperazine Edisylate (Compazine[c]), Chlorpromazine Hydrochloride (Thorazine[c]), Digitoxin (Crystodigin[d]), Digoxin (Lanoxin[e]), Procainamide Hydrochloride (Pronestyl[f]), Triflupromazine Hydrochloride (Vesprin[f]), Promazine Hydrochloride (Sparine[g]).

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[a]Abbott Laboratories, North Chicago, Ill.

[b]Ciba Pharmaceutical Co., Summit, N.J.

[c]Smith, Kline and French Laboratories, Philadelphia, Pa.

[d]Eli Lilly and Co., Indianapolis, Ind.

[e]Burroughs Wellcome and Co., Tuckahoe, N.Y.

[f]E. R. Squibb and Sons, Div., Olin Mathieson Chemical Corp., New York, N.Y.

[g]Wyeth Laboratories, Div., American Home Products Corp., Philadelphia, Pa.

## PRELIMINARY STUDY

U.V. absorption spectra were obtained using the Bausch and Lomb Spectronic 600 Double Beam Spectrophotometer[a]. The spectra obtained were recorded with a Linear/Log Varicord 43 Recorder[b]. The solutions were measured in Bausch and Lomb 33-27-25 Silica Cuvettes using a dueterium lamp to provide an incident beam of wavelength range 200 to 350 millimicrons.

Random dilutions in Sodium Chloride Injection, U.S.P., were made using volumetric flasks, graduated and measuring pipets of suitable size. The absorbances of these solutions were measured using sodium chloride injection as the reference solution. The concentrations necessary to obtain absorbance values of 0.3 to 0.9 was established from the U.V. spectra. Beer's Law curves were plotted for each drug. The U.V. spectrum for each drug alone was considered to be the standard or theoretical results for each parenteral product.

Two problems involved in obtaining spectra for the admixture were the additive effect upon the absorbance and the composite spectrum obtained as a result of having two drugs in solution. Therefore, in order to measure spectral absorbance that would be specific for an individual drug in the admixture, the solution in the reference beam was changed for each measurement. The reference solution contained Drug A in sodium chloride injection at the same concentration as was present in the Drug A + Drug B admixture. The effect of this was to obtain

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[a]Bausch & Lomb Optical Co., Rochester, N.Y.

[b]Photovolt Corp., New York, N.Y.

a spectrum of Drug B that would resemble that of the standard spectrum for Drug B if no change in absorption or if no chemical interaction had occurred. This procedure was reversed to obtain the spectrum for Drug A in the A + B admixture.

## ADMIXTURE ANALYSIS

Without regard to concentration, direct admixture of reconstituted sodium ethacrynate solution with each of the parenteral solutions under investigation was made. Two drops of sodium ethacrynate were mixed with two drops of the combining drug on a microscope slide and examined immediately for the presence of particulate matter. The presence of particulate matter was indicative of a physical interaction.

Admixtures of sodium ethacrynate with each of the parenteral products listed above were prepared in sodium chloride injection in therapeutic concentration. An admixture of therapeutic concentrations was considered to be a therapeutic dose added to 1000 milliliters of infusion fluid (See Table XI). When the capabilities of the spectrophotometer would permit, therapeutic admixtures were used to obtain the U.V. spectrum for each drug in the combination. As already indicated, the reference solution used was the corresponding drug in sodium chloride injection at the same concentration as that of the drug in the admixture.

In those instances where the therapeutic concentration of the admixture could not be measured spectrophotometrically because of too high an absorbance, appropriate dilutions of the original admixture were made to obtain absorbance values within the above-mentioned range.

All measurements were performed in triplicate and the pH of each solution

was obtained using the Corning Model 7 pH Meter[a]. The U.V. spectra were obtained at one, four, and eight hours after the therapeutic admixtures had been prepared. The results of these spectrophotometric measurements of the admixtures were compared with the standard spectrum of each parenteral product alone to detect any change in the absorption due to the added drug.

The spectra obtained are shown in the various figures which follow. The admixture concentration, $\lambda$max, reference solution, and the time at which the measurement was made are included in the legends accompanying the U.V. spectra. The standard spectra were obtained using the drug at the same concentration as that of the admixture. The changes in the pH of the admixtures solutions are listed in the tables which follow. The values listed are averages of replicate measurements. The diluting solution was sodium chloride injection.

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[a]Corning Scientific Instruments, Cambridge, Mass.

## III. RESULTS

The results of the experimental findings as described in this chapter refer to admixtures prepared in Sodium Chloride Injection, U.S.P., at the concentrations indicated. These results include mean values of three replicate determinations. No appreciable change occurred with respect to time, and for this reason, no further mention of time as a variable will be made.

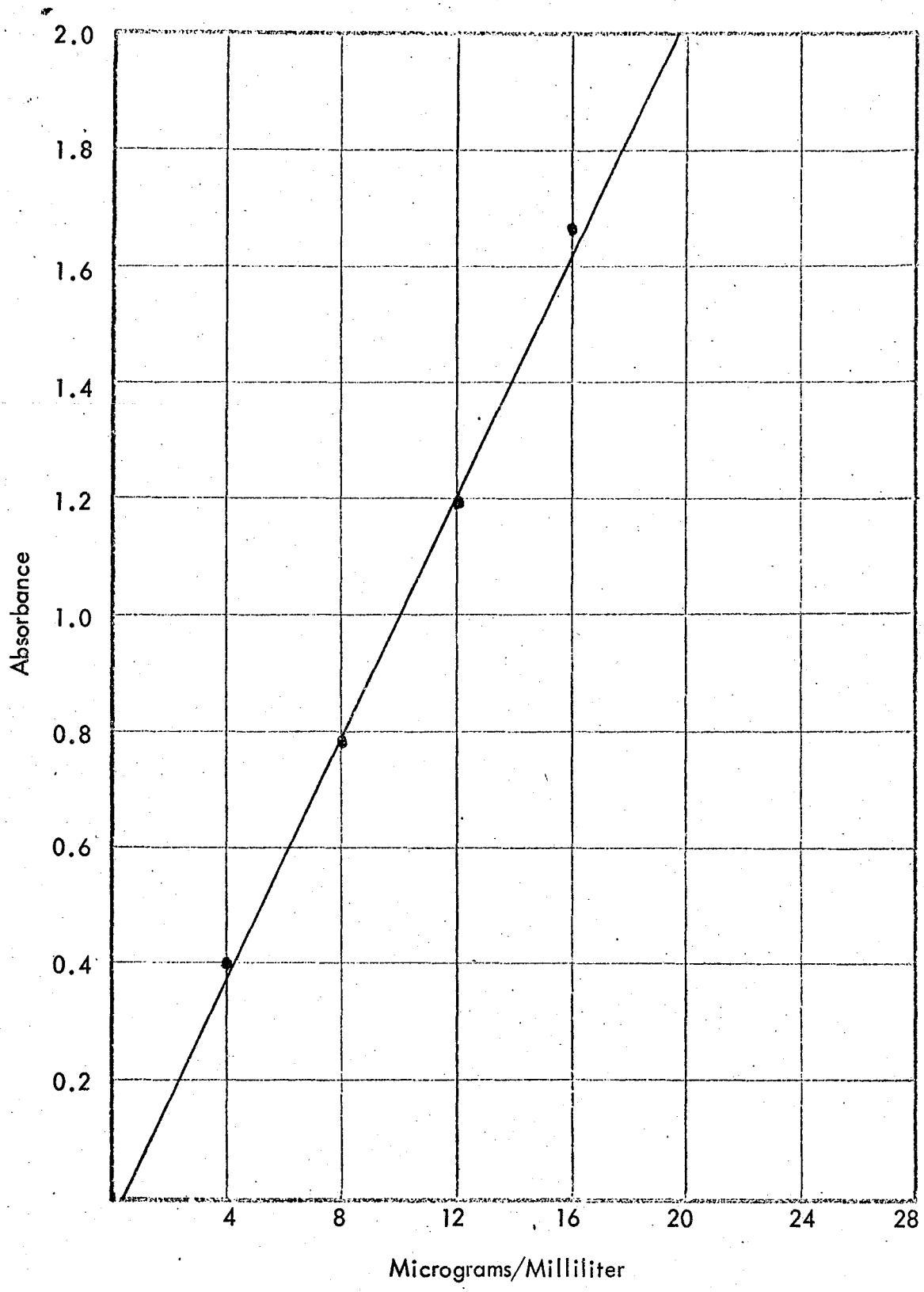
### Chlorpromazine Hydrochloride-Sodium Ethacrynate

A solution containing therapeutic concentrations of sodium ethacrynate, 50mcg./ml. and chlorpromazine hydrochloride, 50 mcg./ml., was prepared. To obtain optimum results, appropriate dilutions were made to achieve a concentration of 40 mcg./ml. and 8mcg./ml., respectively. Neither spectrum was altered and the absorbance did not decrease to a significant extent during the eight hour study (See Fig. 1-3). These data would seem to indicate the absence of chemical interaction. The undiluted admixture of each drug on a microscope slide resulted in a cloudy solution, indicative of a physical interaction. The results of the pH determination are listed in Table I.

TABLE I

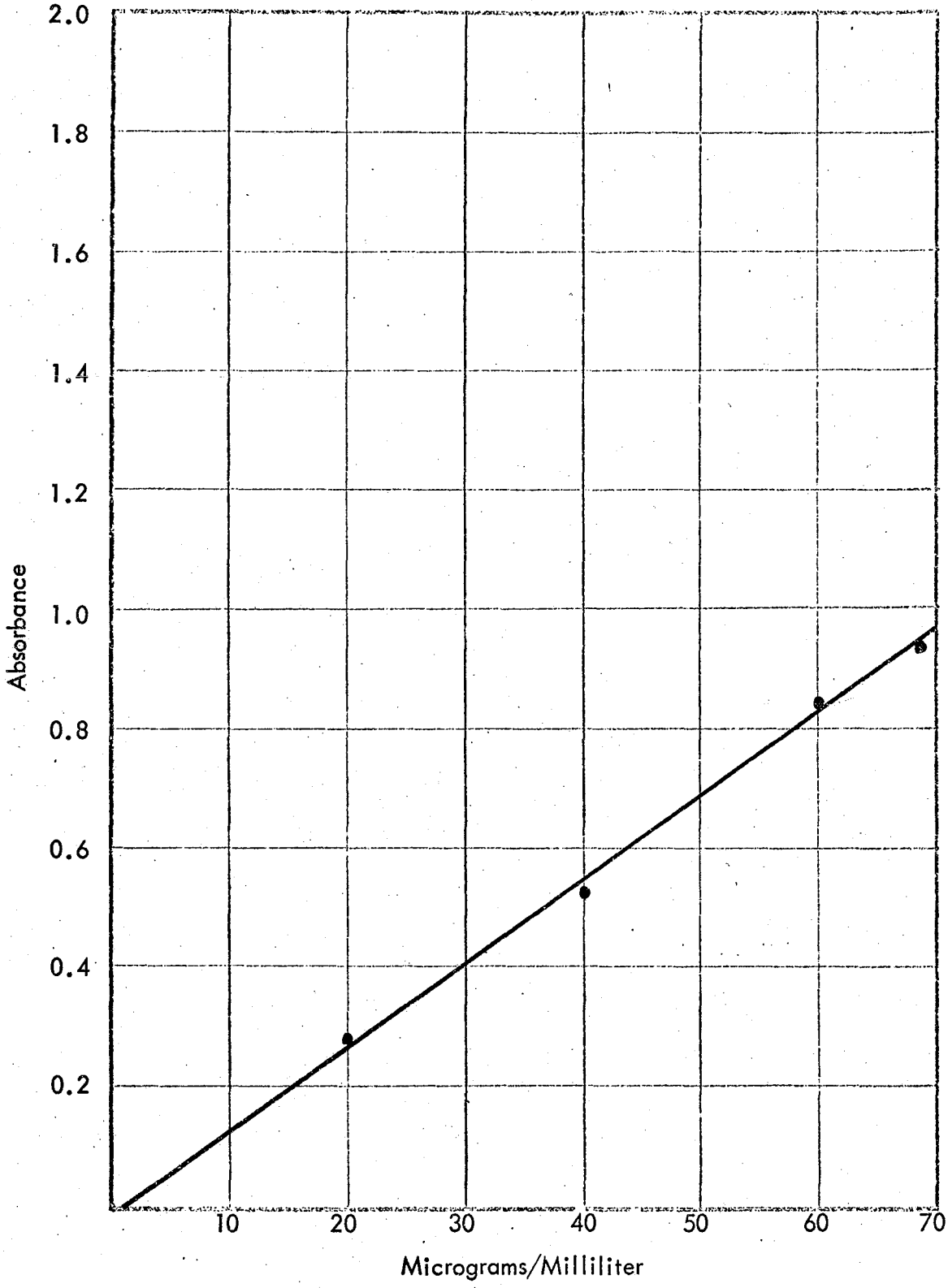
Change in pH of Chlorpromazine Hydrochloride-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Chlorpromazine Hydrochloride, 50mcg./ml. | 3.6 | 3.6 | 3.5 |
| Therapeutic Admixture | 6.7 | 6.3 | 6.1 |
| Dilution | 6.9 | 6.4 | 6.2 |



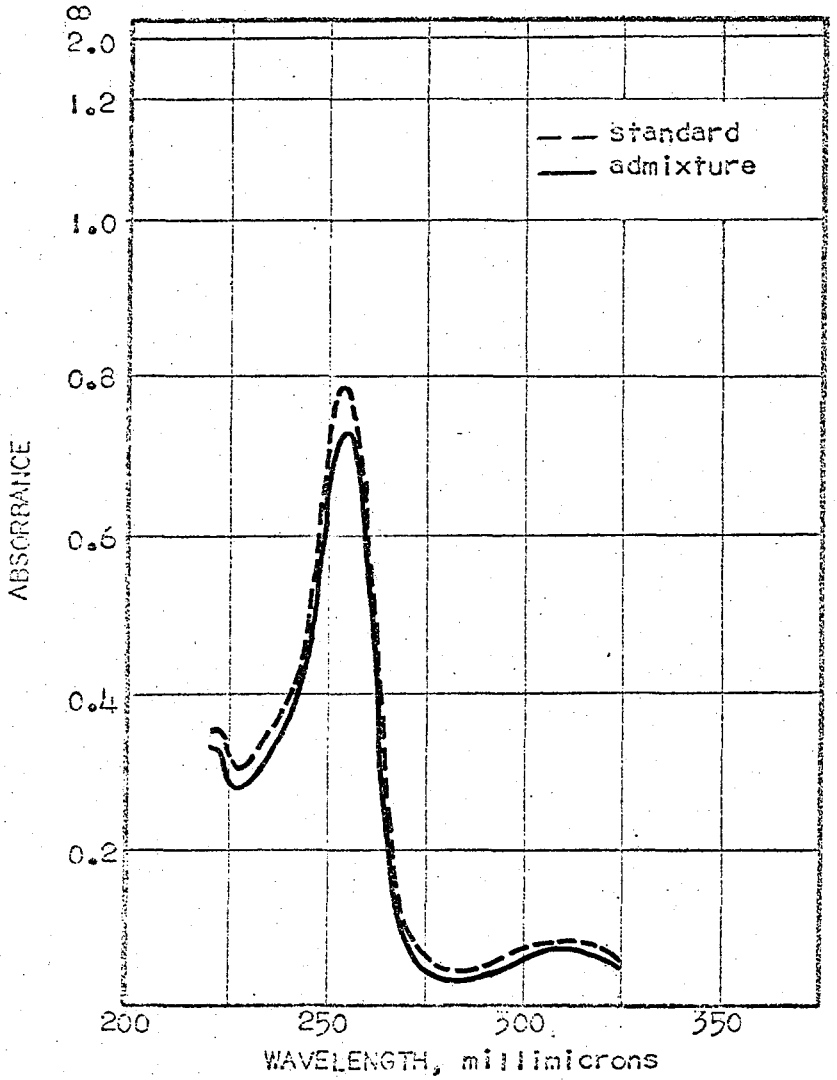

Graph 1

Standard Curve for Chlorpromazine Hydrochloride

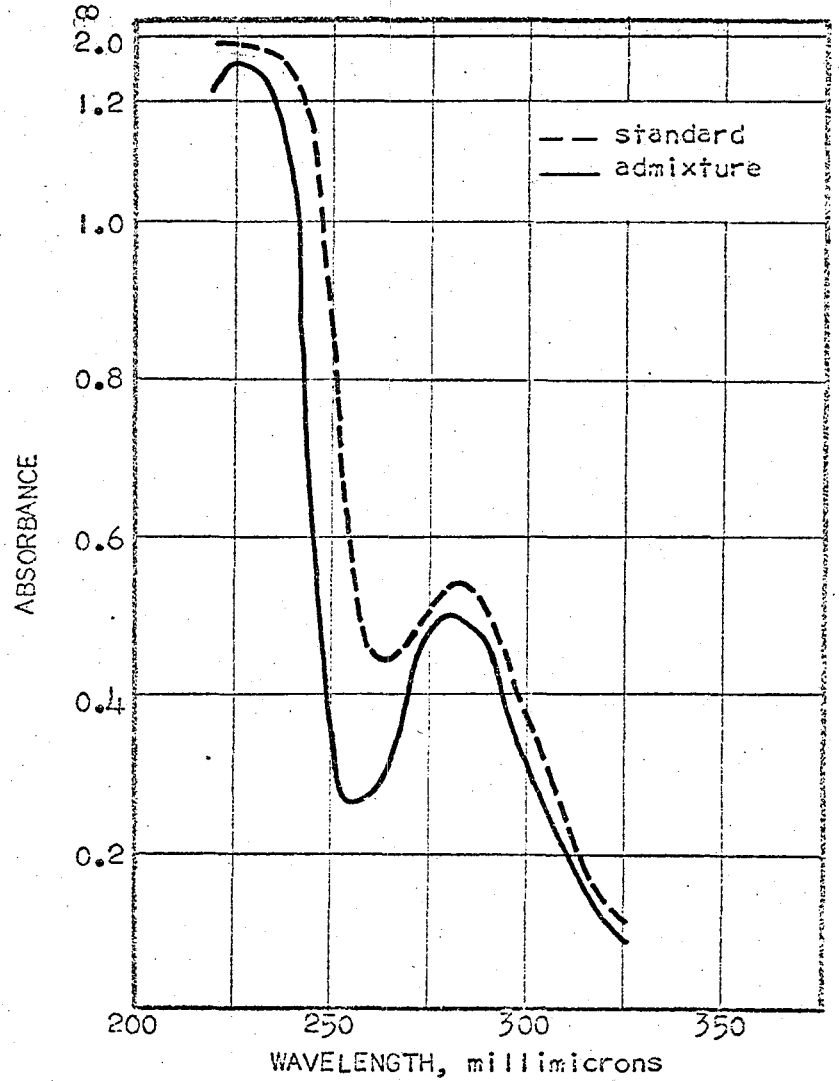



Graph 2

Standard Curve for Sodium Ethacrynate

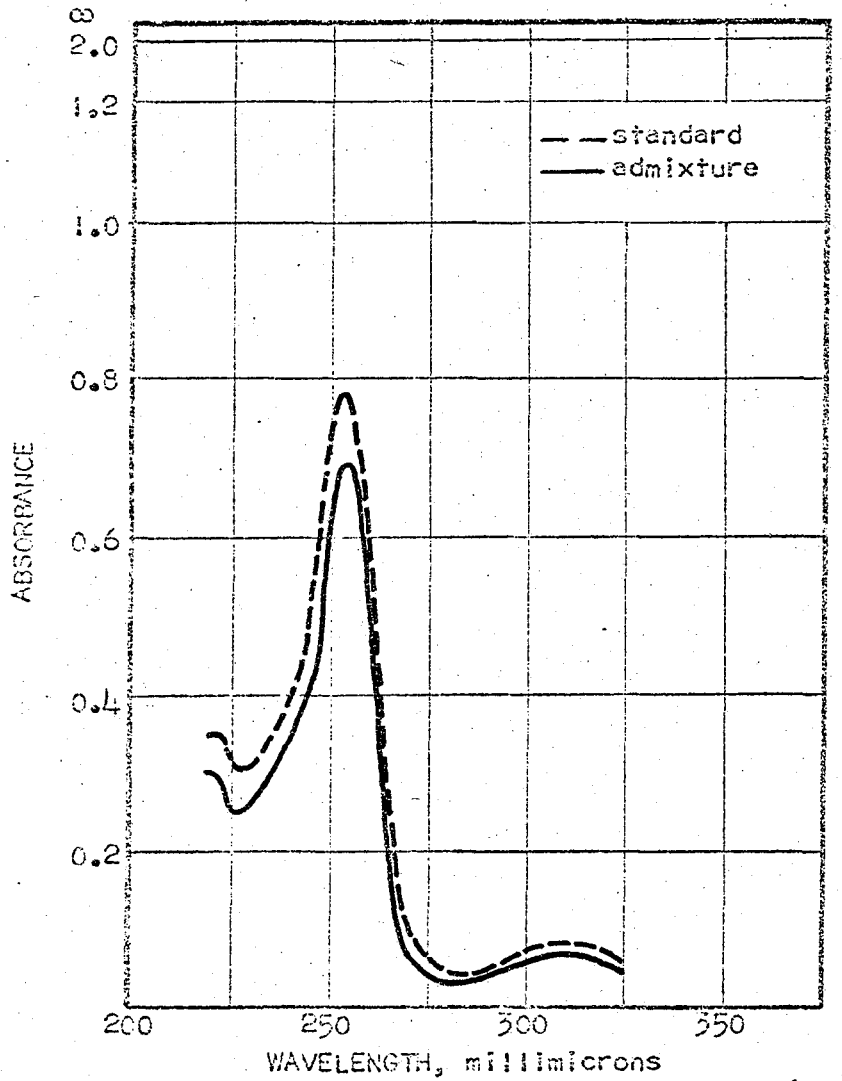



Chlorpromazine Hydrochloride, 8mcg./ml.
Ref. Sodium Ethacrynate, 8mcg./ml.

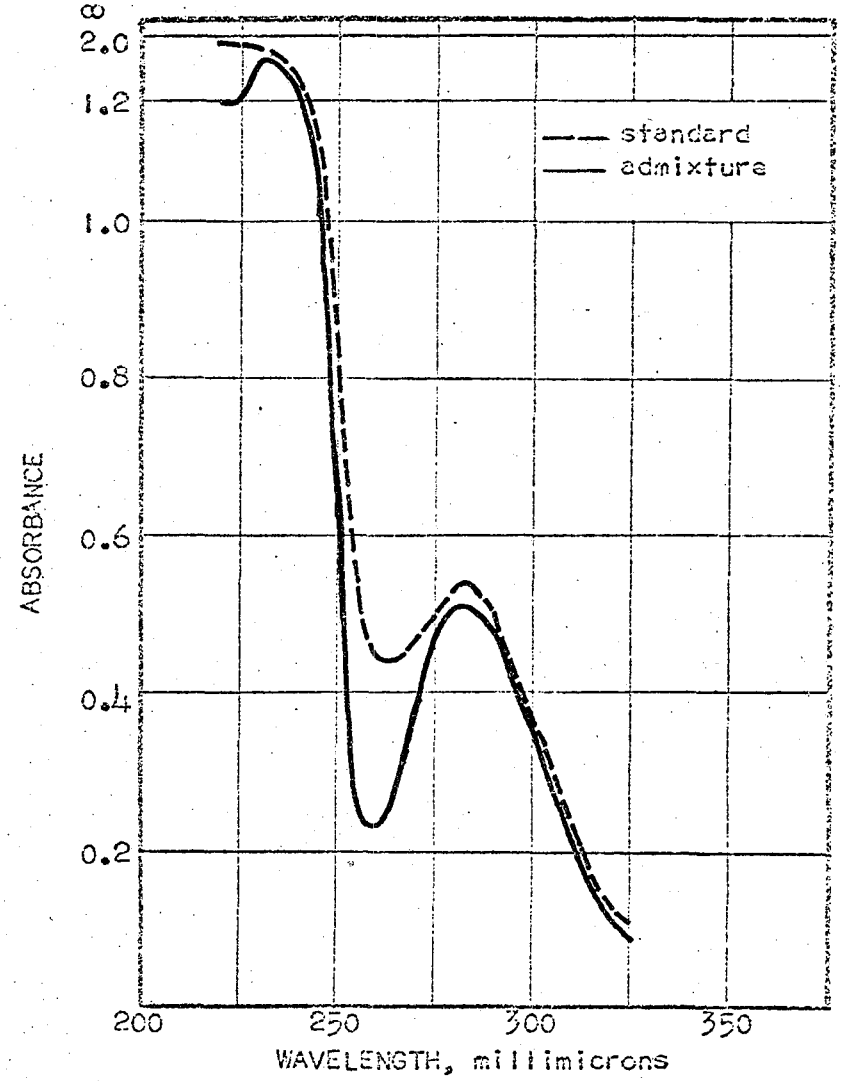



Sodium Ethacrynate, 40mcg./ml.
Ref. Chlorpromazine Hydrochloride, 40 mcg./ml.

Fig. 1. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$ max 280) with Chlorpromazine Hydrochloride ( $\lambda$ max 255) at 1 Hour.

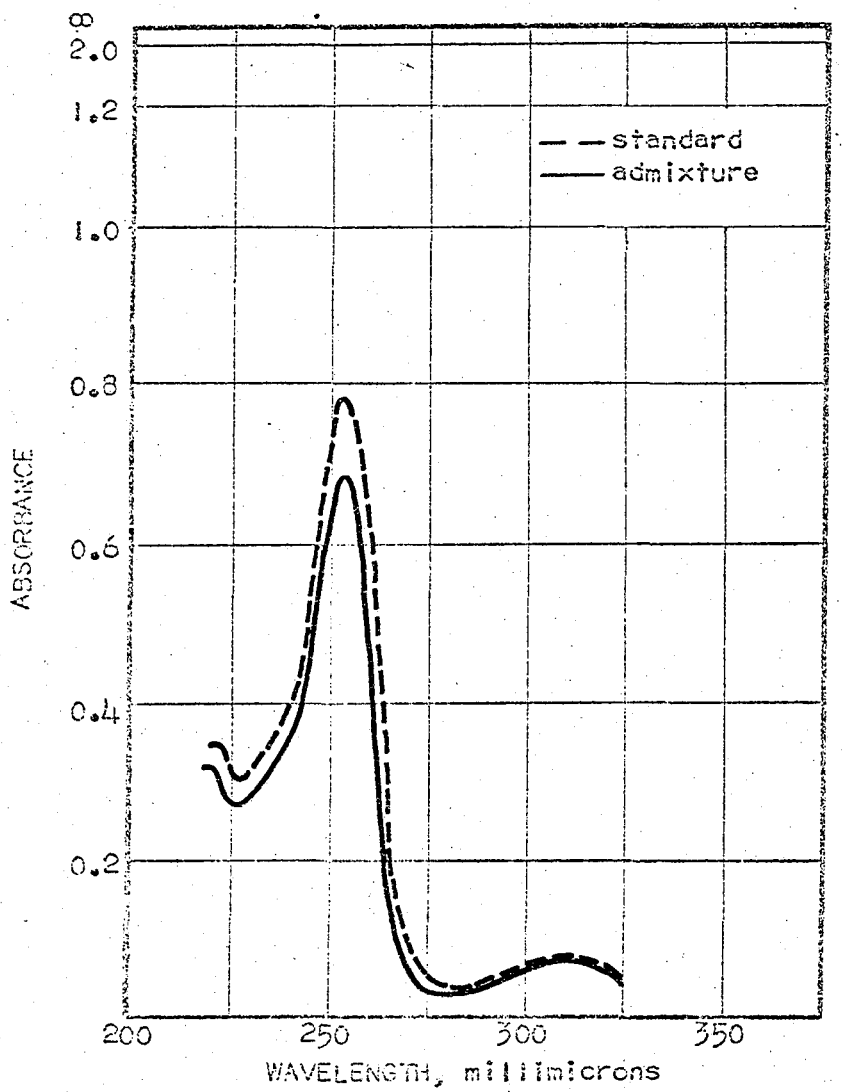



Chlorpromazine Hydrochloride, 8 mcg./ml.
Ref. Sodium Ethacrynate, 8mcg./ml.

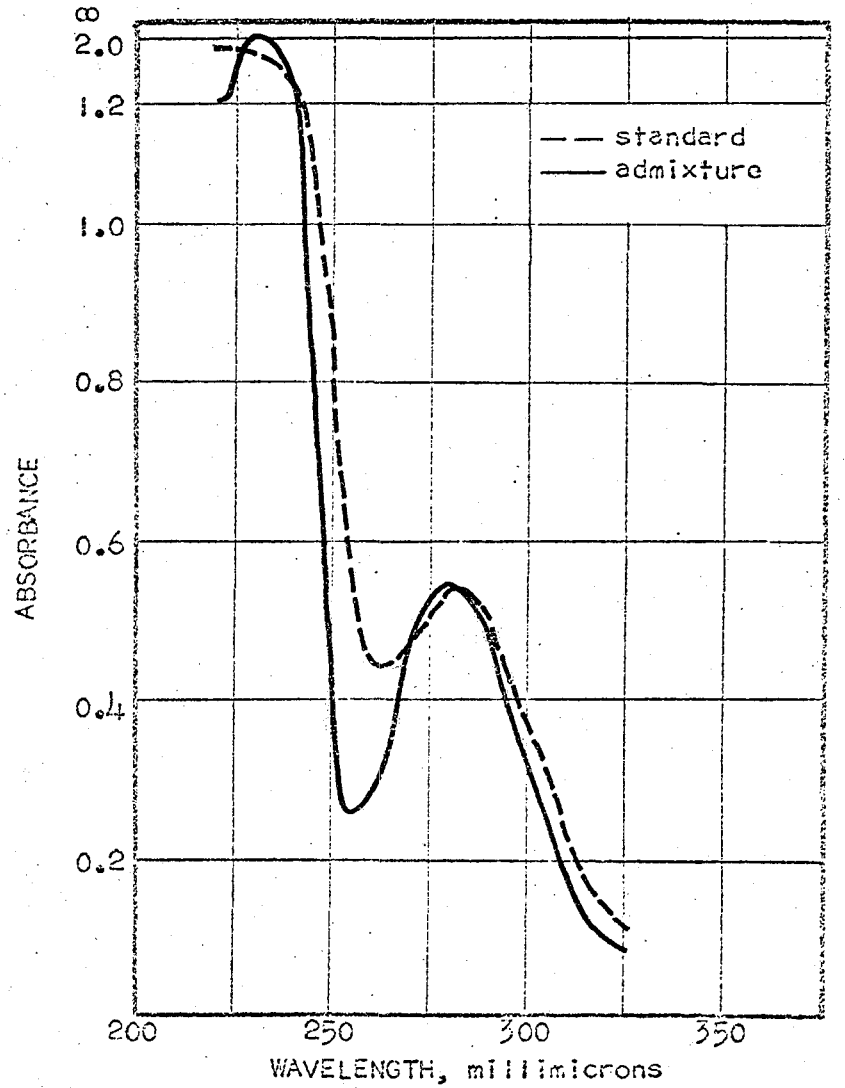



Sodium Ethacrynate, 40mcg./ml.
Ref. Chlorpromazine Hydrochloride, 40mcg./ml.

Fig. 2. U.V. Spectra of Admixture of Sodium Ethacrynate ( λmax 280) with Chlorpromazine Hydrochloride ( λmax 255) at 4 Hours.




Chlorpromazine Hydrochloride, 8 mcg./ml.
Ref. Sodium Ethacrynate, 8 mcg./ml.




Sodium Ethacrynate, 40 mcg./ml.
Ref. Chlorpromazine Hydrochloride, 40 mcg./ml.

Fig. 3. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$ max 280) with Chlorpromazine Hydrochloride ( $\lambda$ max 255) at 8 Hours.

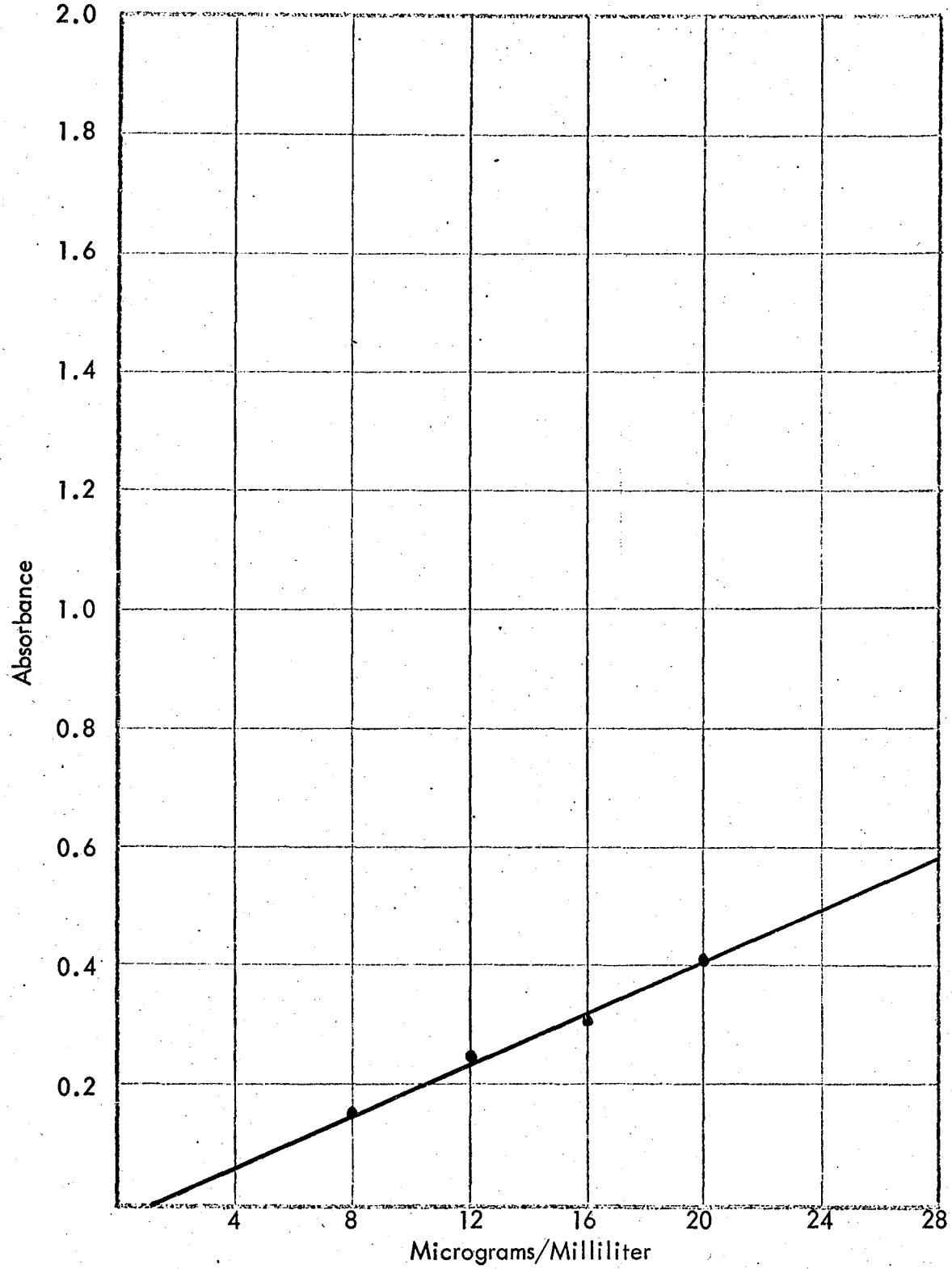
Digitoxin-Sodium Ethacrynate

The absorption spectrum of sodium ethacrynate in the presence of digitoxin was obtained using therapeutic concentrations of each, 50mcg./ml. and 0.2mcg./ml., respectively. To obtain an optimum measurement for digitoxin, a solution containing 20mcg./ml. of digitoxin and 50mcg./ml. of sodium ethacrynate was prepared. The spectrum for sodium ethacrynate was not altered appreciably during the eight hour period (See Fig. 4-6), while that of digitoxin exhibited a loss in absorbance at the $\lambda$ max in comparison to that of digitoxin alone (See Fig. 4-6). The loss in absorbance indicates a decrease in the concentration of digitoxin of approximately 40 per cent and was great enough to suggest a chemical interaction. Undiluted admixture of these two drugs on a microscope slide resulted in a clear solution, indicative of a physical compatibility. The results of the pH determination are listed in Table II.

TABLE II

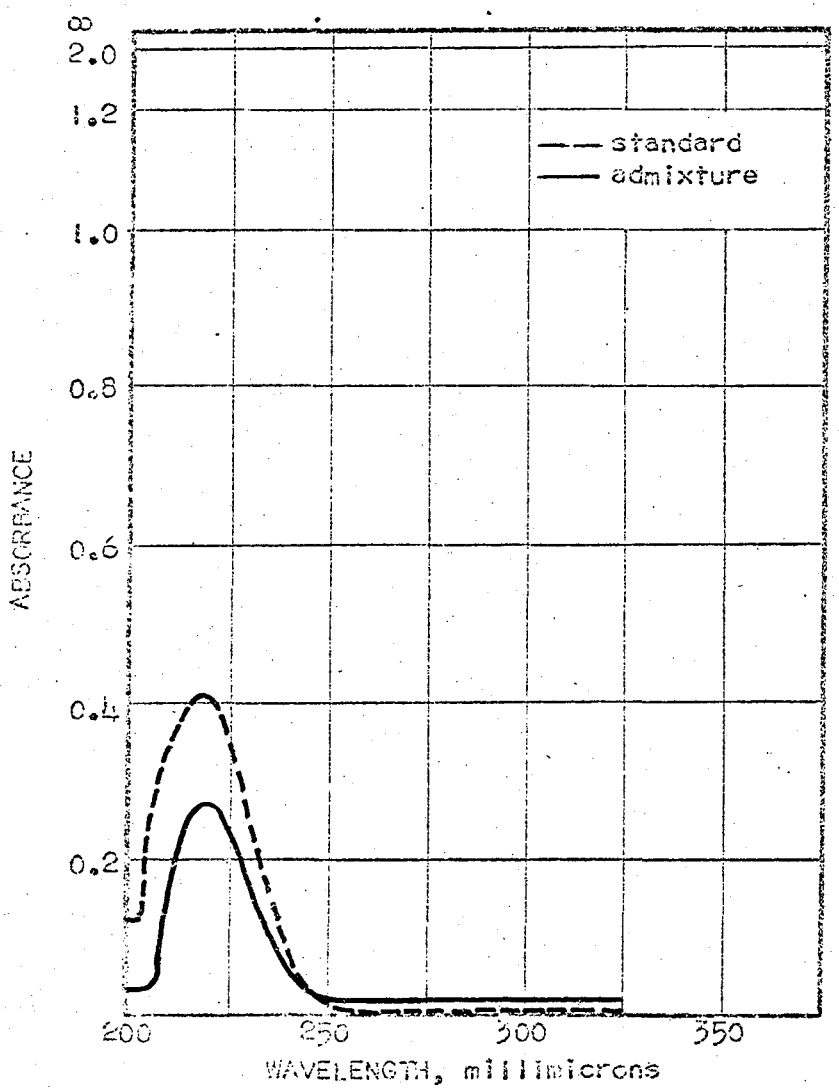
Change in pH of Digitoxin-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Digitoxin, 0.2mcg./ml. | 4.4 | 4.2 | 4.1 |
| Therapeutic Admixture | 6.0 | 5.8 | 6.0 |
| Dilution | 6.1 | 5.9 | 6.1 |

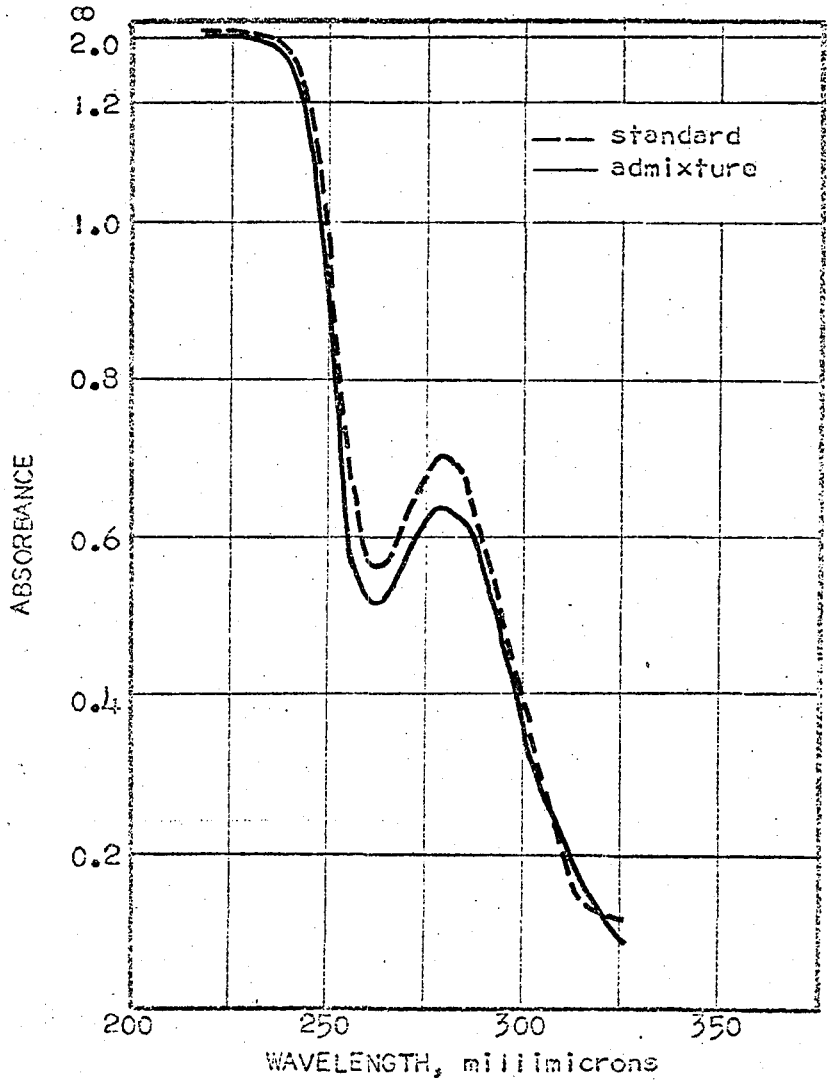



Graph 3

Standard Curve for Digitoxin

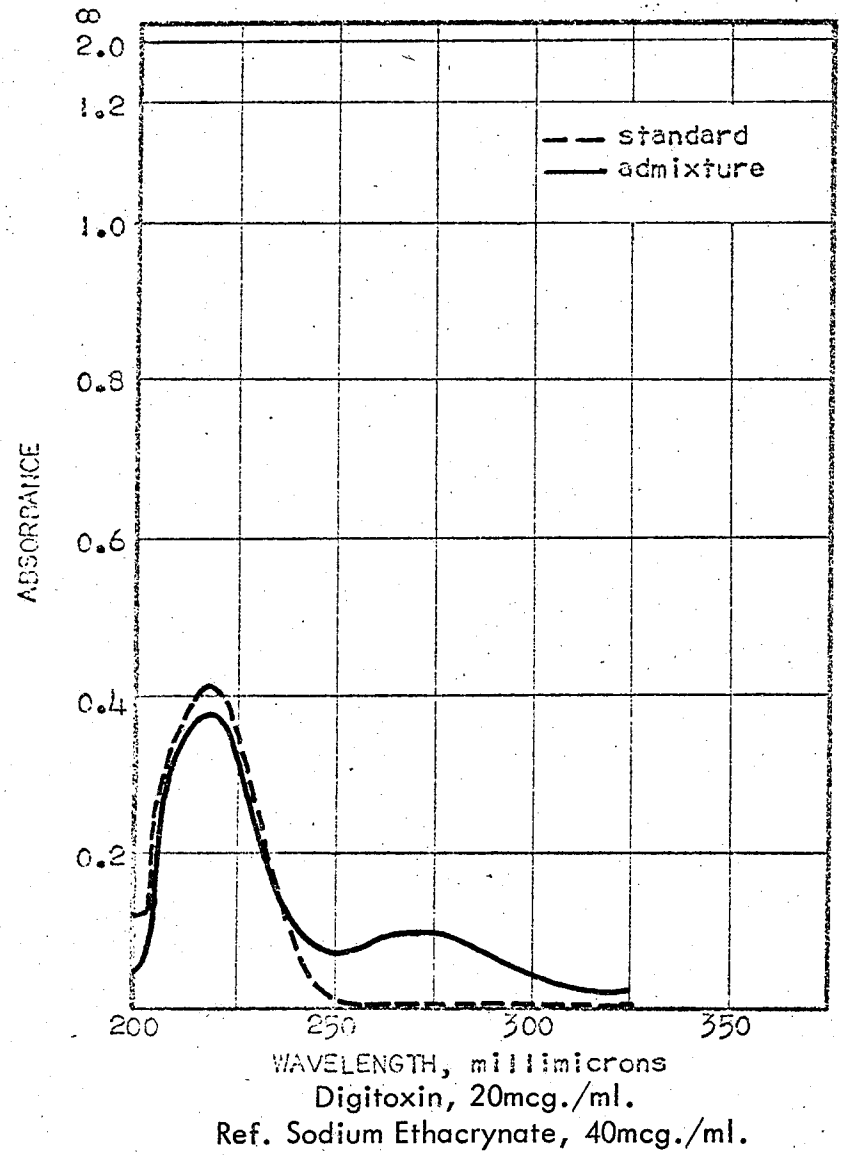



Digitoxin, 20mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

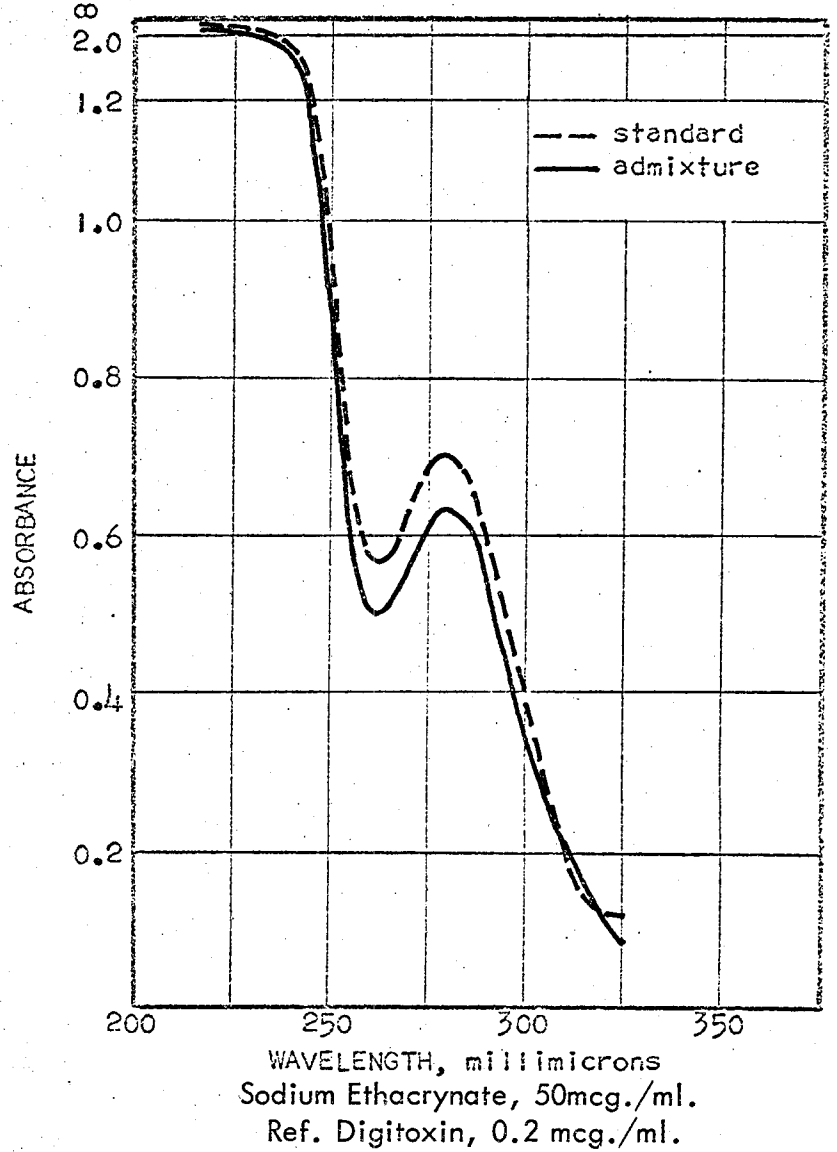



Sodium Ethacrynate, 50mcg./ml.
Ref. Digitoxin, 0.2mcg./ml.

Fig. 4. U.V. Spectra of Admixture of Sodium Ethacrynate ( λmax 280) with Digitoxin ( λmax 222) at 1 Hour.

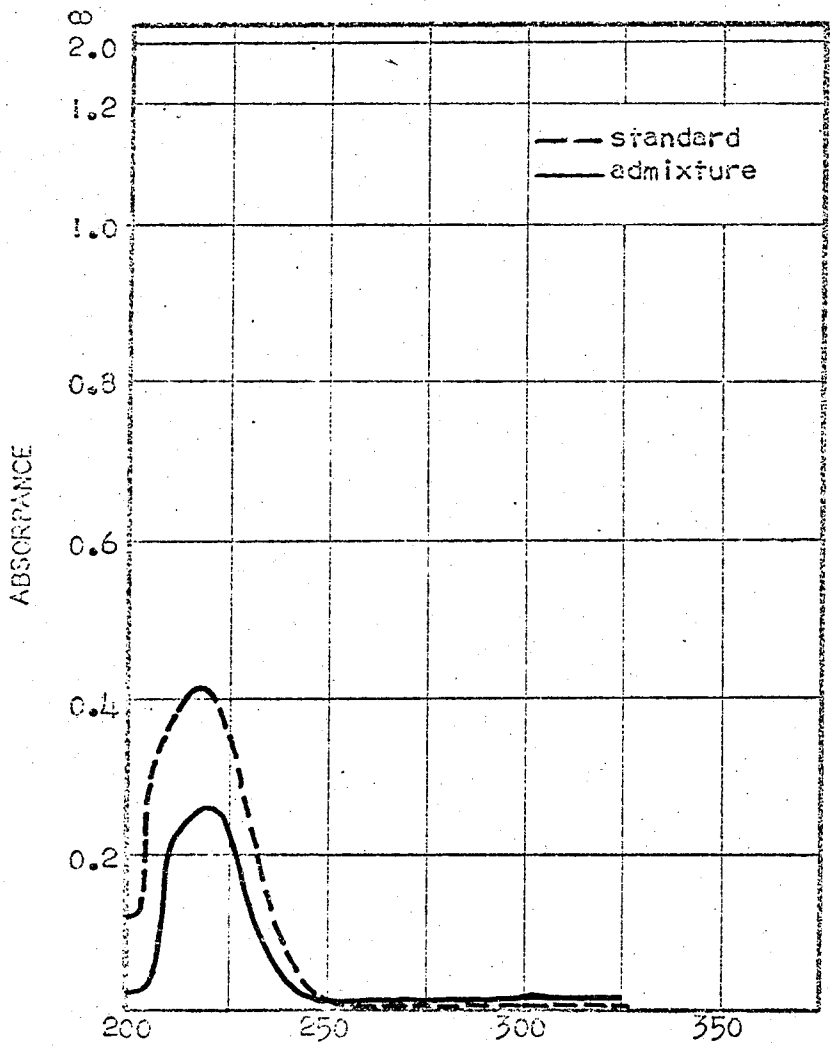



Digitoxin, 20mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

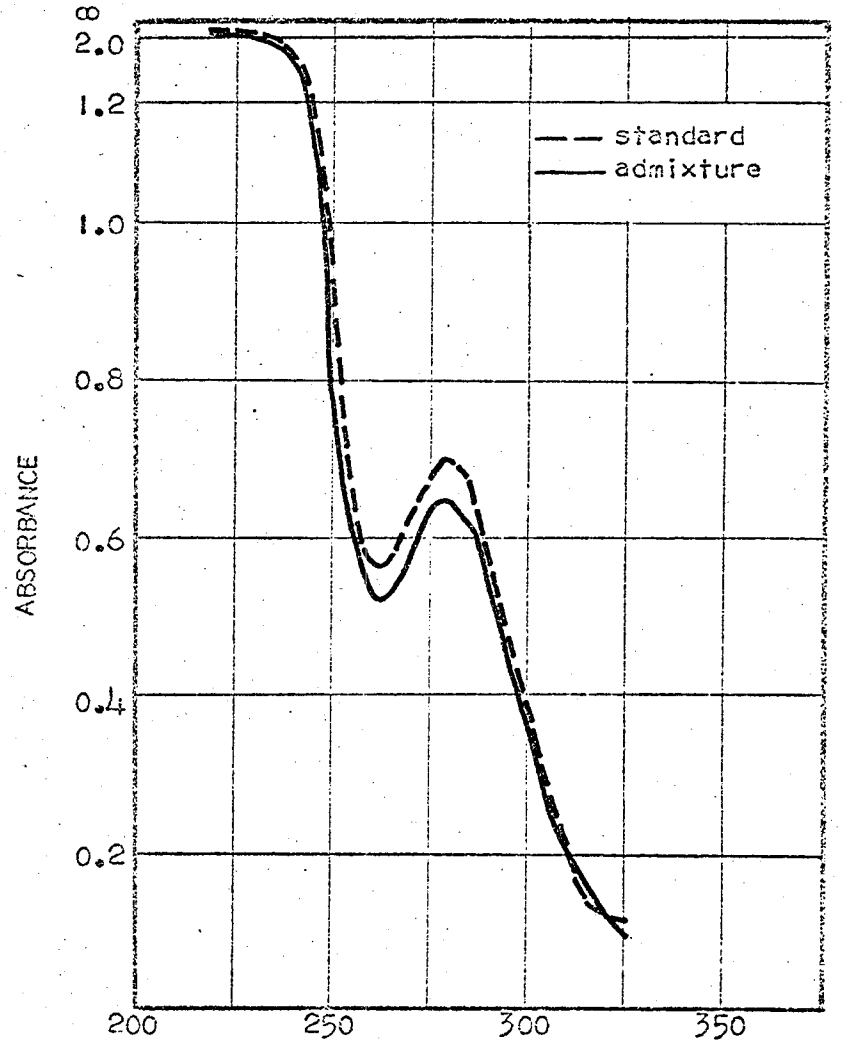



Sodium Ethacrynate, 50mcg./ml.
Ref. Digitoxin, 0.2 mcg./ml.

Fig. 5. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$max 280) with Digitoxin ( $\lambda$ max 222) at 4 Hours.




Digitoxin, 20 mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.




Sodium Ethacrynate, 50mcg./ml.
Ref. Digitoxin, 0.2mcg./ml.

Fig. 6. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$ max 280) with Digitoxin ($\lambda$ max 222) at 8 Hours.

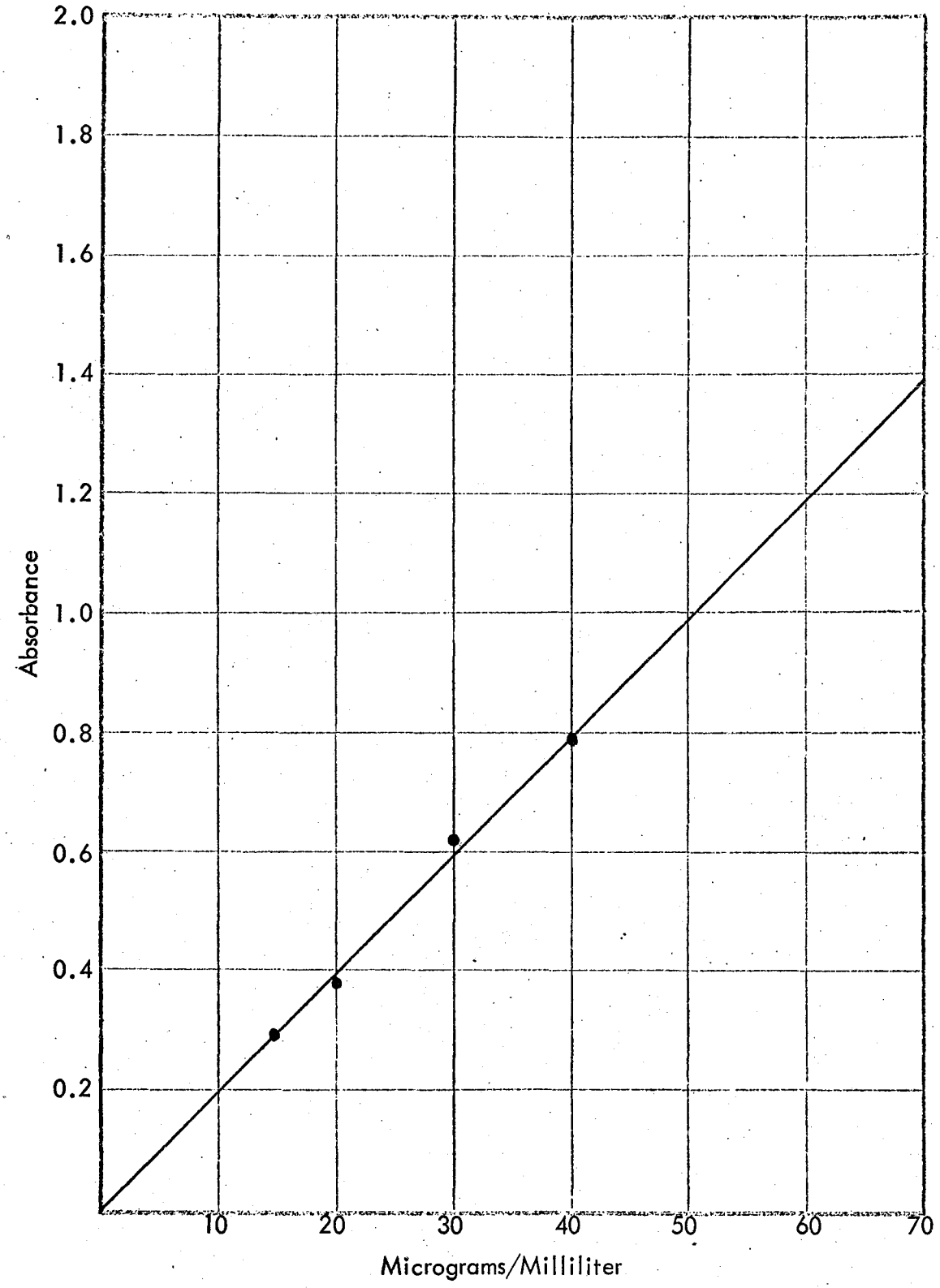
Digoxin-Sodium Ethacrynate

Undiluted admixture of sodium ethacrynate and digoxin resulted in a clear solution, indicative of a physical compatibility, while the spectrophotometric measurements of the admixture at therapeutic concentrations provided results suggestive of a chemical interaction. The absorption spectrum of sodium ethacrynate in the presence of digoxin was obtained using therapeutic concentrations of each, 50mcg./ml., and 1mcg./ml., respectively. To obtain optimum absorbance for digoxin, a solution containing 40mcg./ml. of each parenteral product was prepared. The spectrum for sodium ethacrynate was not altered appreciably throughout the eight hour study (See Fig. 7-9), while that of digoxin exhibited a loss in absorbance at the $\lambda$max in comparison to that of the digoxin reference (See Fig. 7-9). From the Beer's Law data, this loss amounted to approximately 40 per cent decrease in concentration, and was significant enough to suggest a chemical interaction. The results of the pH determination are listed in Table III.

TABLE III

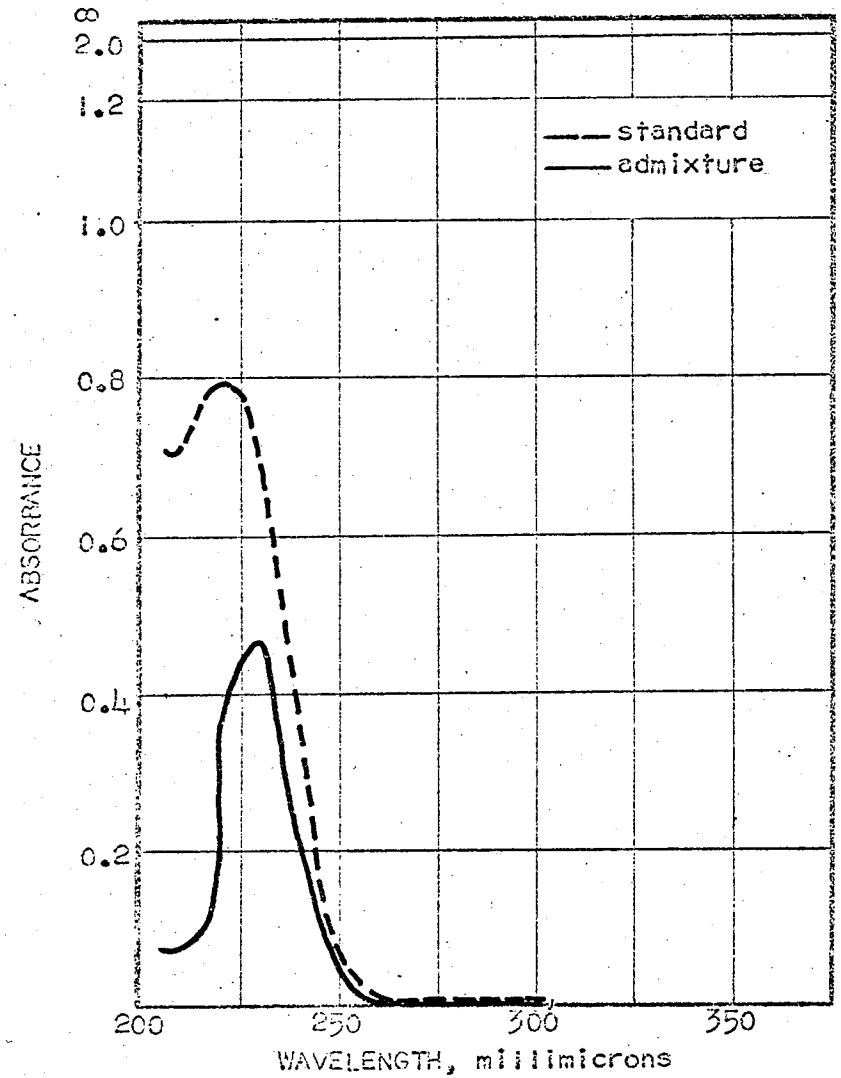
Change in pH of Digoxin-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Digoxin, 1mcg./ml. | 3.3 | 3.5 | 3.5 |
| Therapeutic Admixture | 6.1 | 6.2 | 5.8 |
| Dilution | 6.0 | 6.2 | 6.0 |

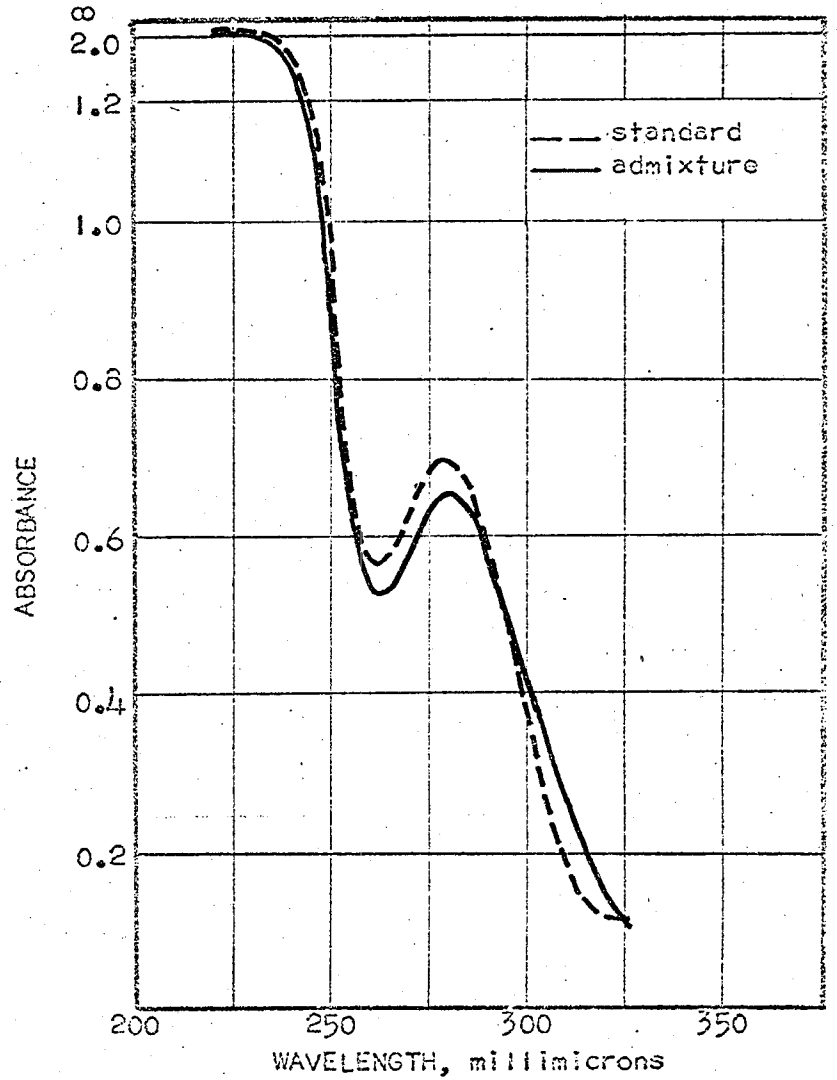



Graph 4

Standard Curve for Digoxin

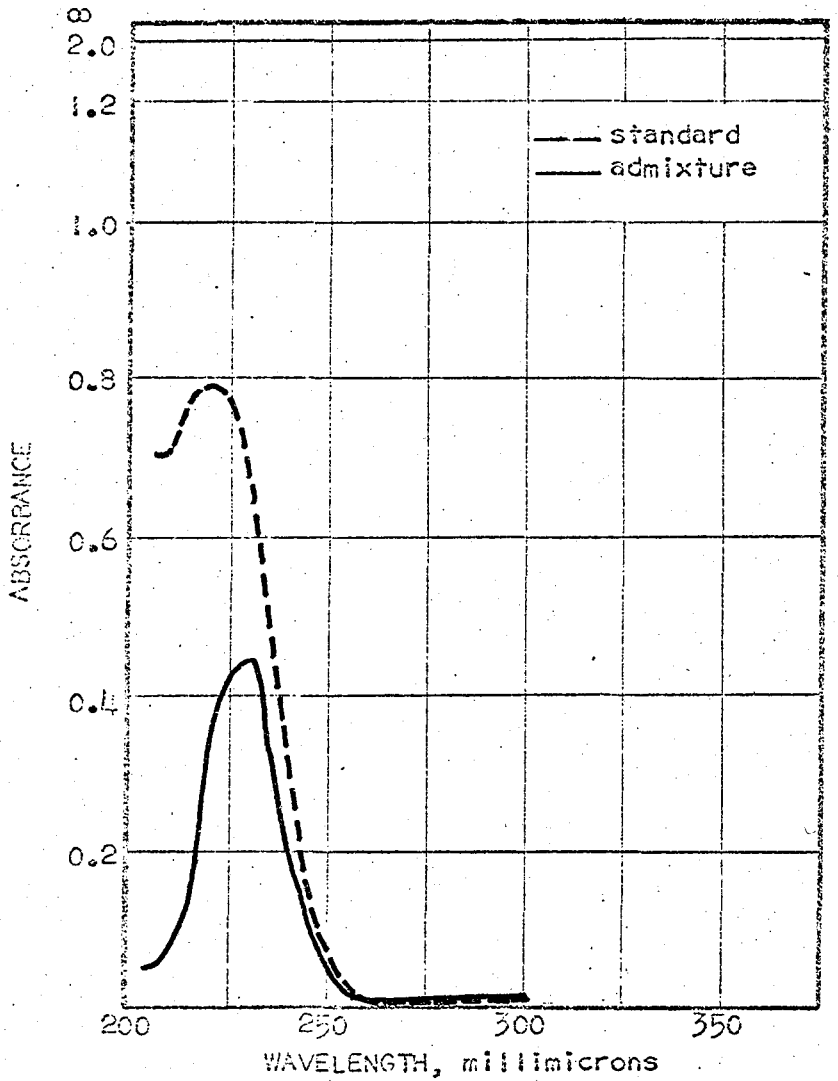



Digoxin, 40mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

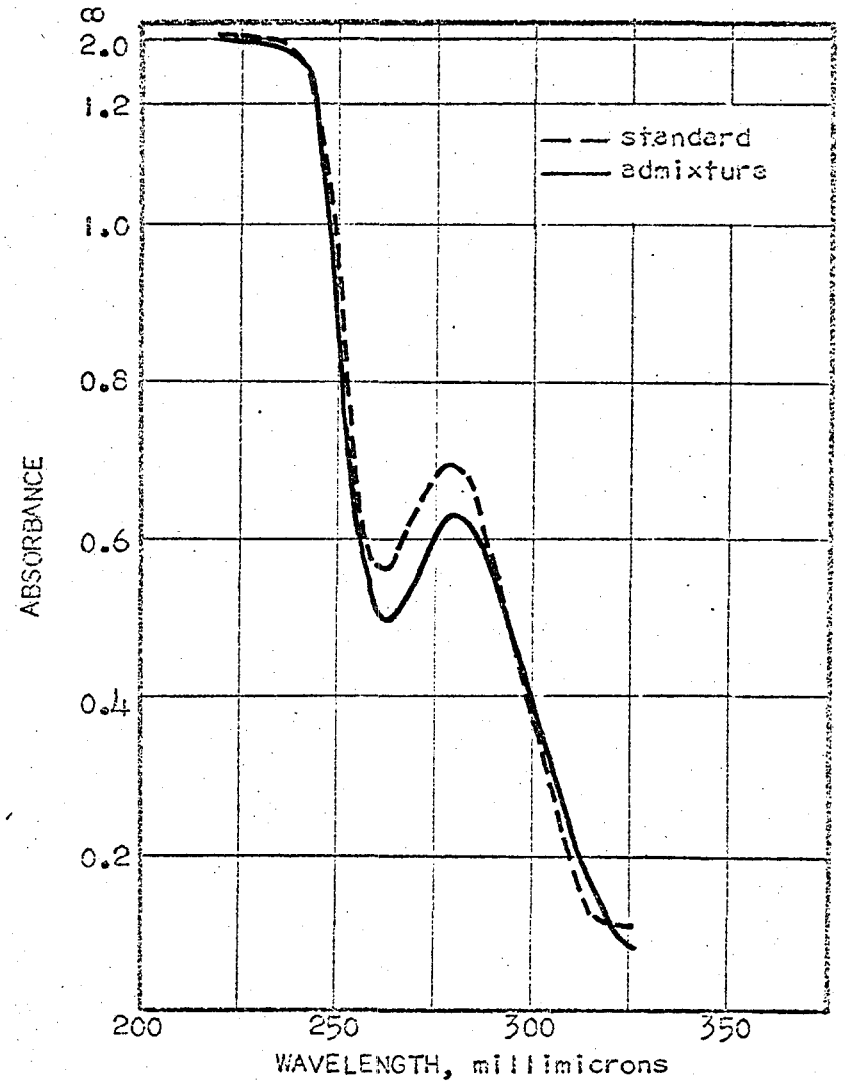



Sodium Ethacrynate, 50mcg./ml.
Ref. Digoxin, 1mcg./ml.

Fig. 7. U.V. Spectra of Admixture of Sodium Ethacrynate ( λmax 280) with Digoxin ( λ max 220) at 1 Hour.

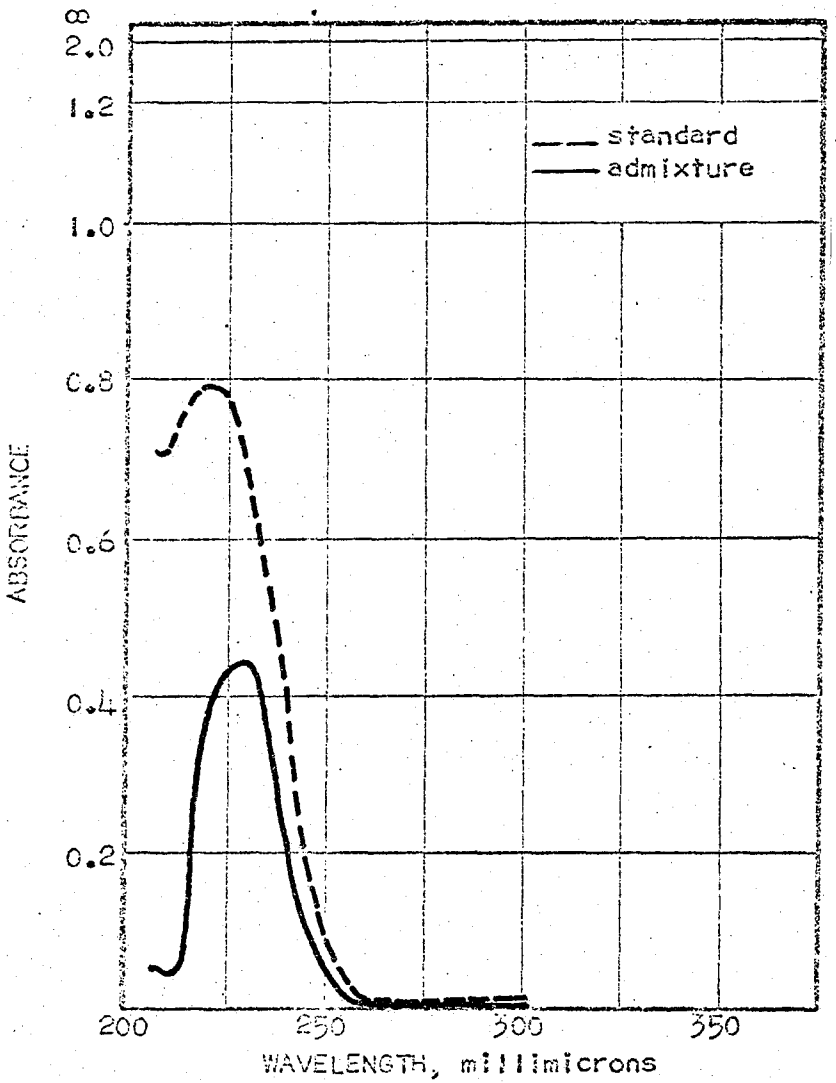



Digoxin, 40mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

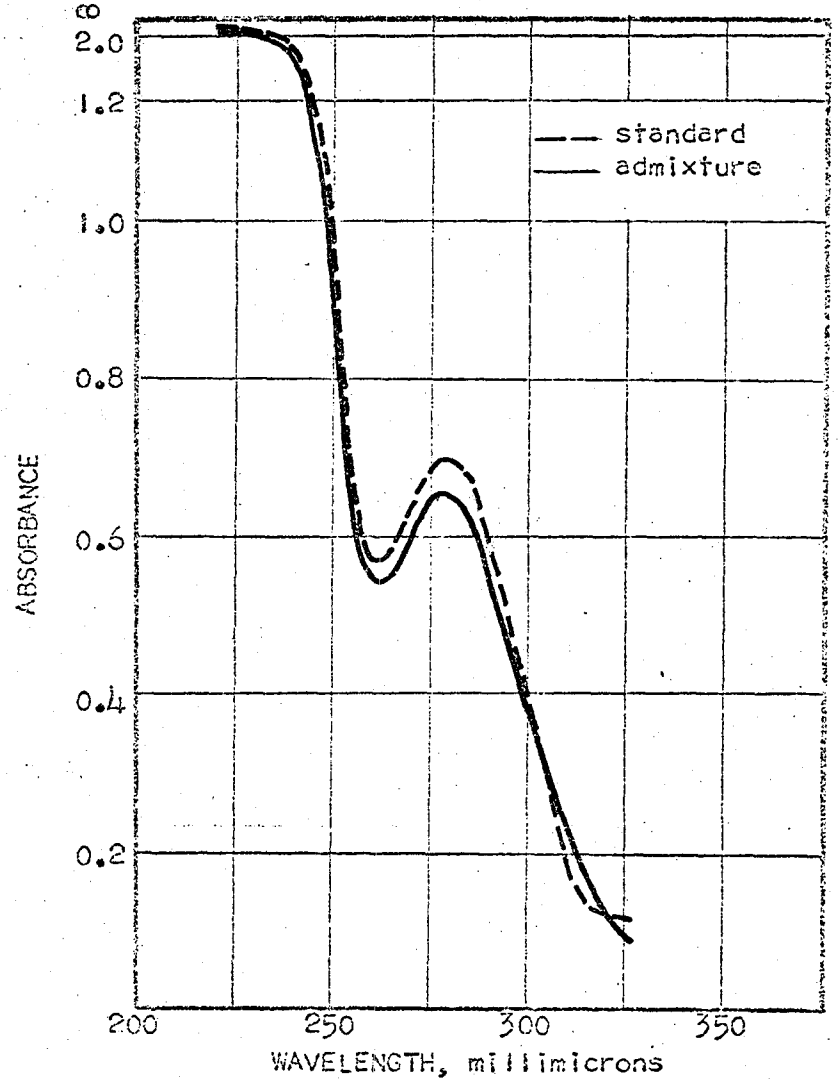



Sodium Ethacrynate, 50mcg./ml.
Ref. Digoxin, 1mcg./ml.

Fig. 8. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$ max 280) with Digoxin ( $\lambda$ max 220) at 4 Hours.




Digoxin, 40mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.




Sodium Ethacrynate, 50mcg./ml.
Ref. Digoxin, 1mcg./ml.

Fig. 9. U.V. Spectra of Admixture of Sodium Ethacrynate ( λmax 280) with Digoxin ( λmax 220) at 8 Hours.

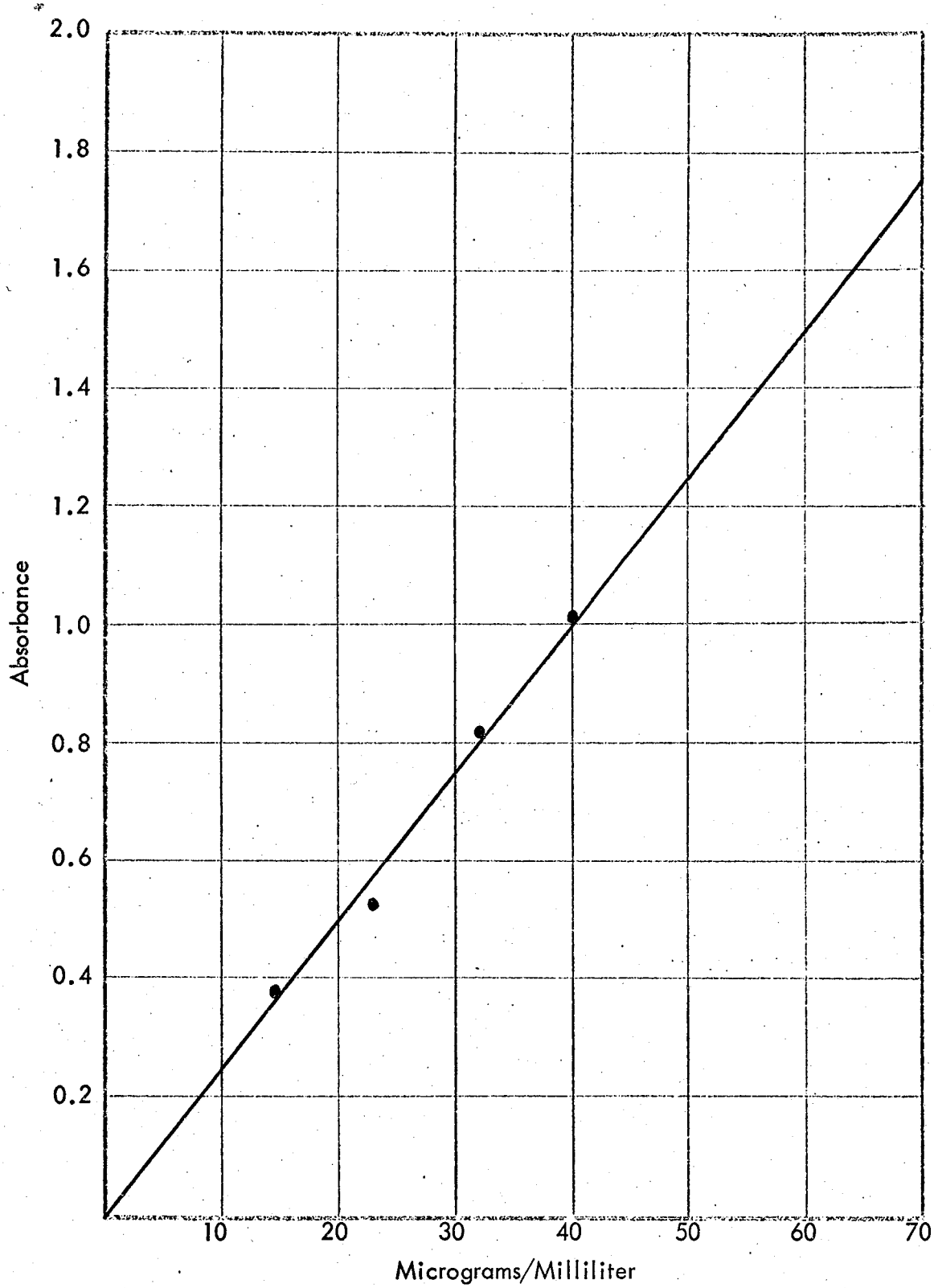
Hydralazine Hydrochloride-Sodium Ethacrynate

Preparation of an admixture of therapeutic concentration of sodium ethacrynate and hydralazine hydrochloride with subsequent spectrophotometric measurement indicated a chemical interaction. Undiluted admixture resulted in a clear solution, indicative of a physical compatibility. Sodium ethacrynate and hydralazine hydrochloride were mixed in therapeutic concentrations, 50mcg./ml. and 20mcg./ml., respectively. The limitations of the spectrophotometer prevented using this solution directly and, therefore, appropriate dilutions were made to achieve the optimum concentration of 40mcg./ml. and 16mcg./ml., respectively. The absorption spectrum obtained for sodium ethacrynate in the admixture did not resemble the reference spectrum (See Fig. 10-12). This is indicative of a change in the chemical nature of the additives and may be due to a chemical interaction. The results of the pH determination are listed in Table IV.

TABLE IV

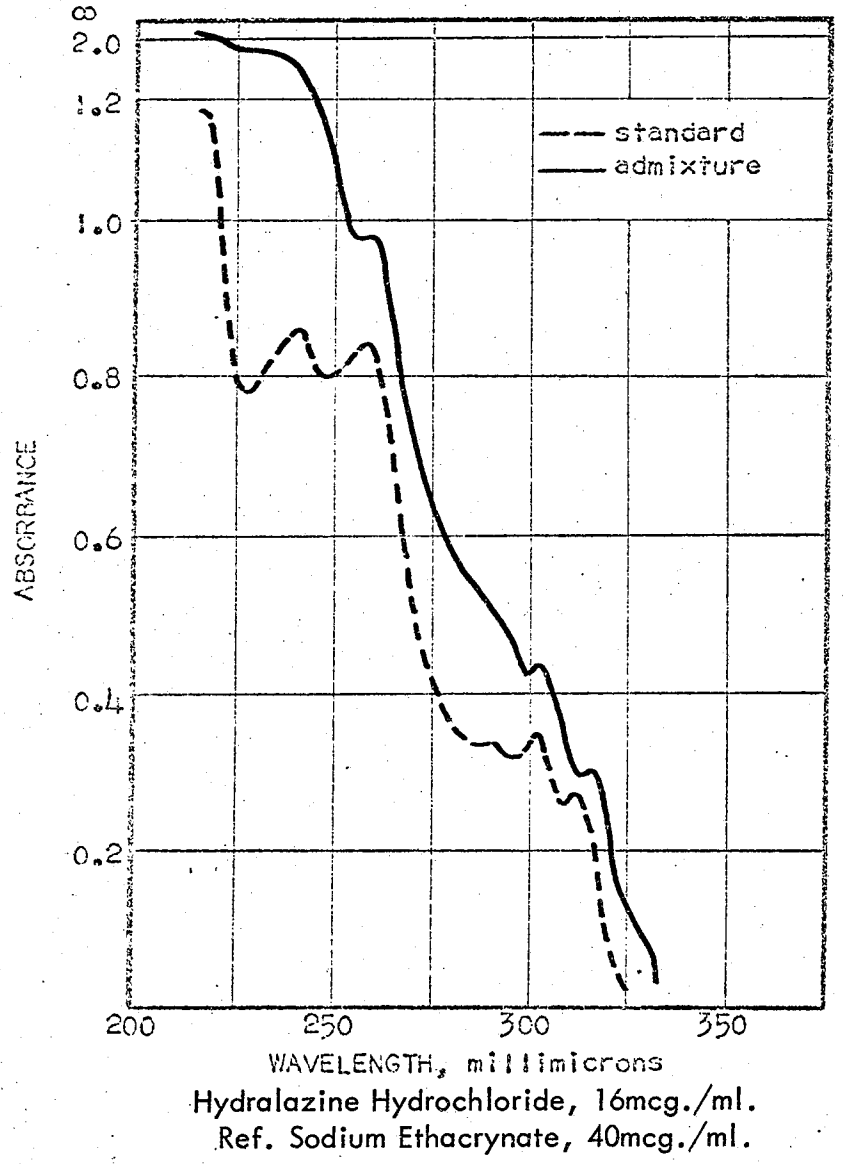
Change in pH of Hydralazine Hydrochloride-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Hydralazine Hydrochloride, 40mcg./ml. | 5.0 | 4.7 | 4.8 |
| Therapeutic Admixture | 6.1 | 6.2 | 5.8 |
| Dilution | 6.0 | 6.2 | 6.0 |

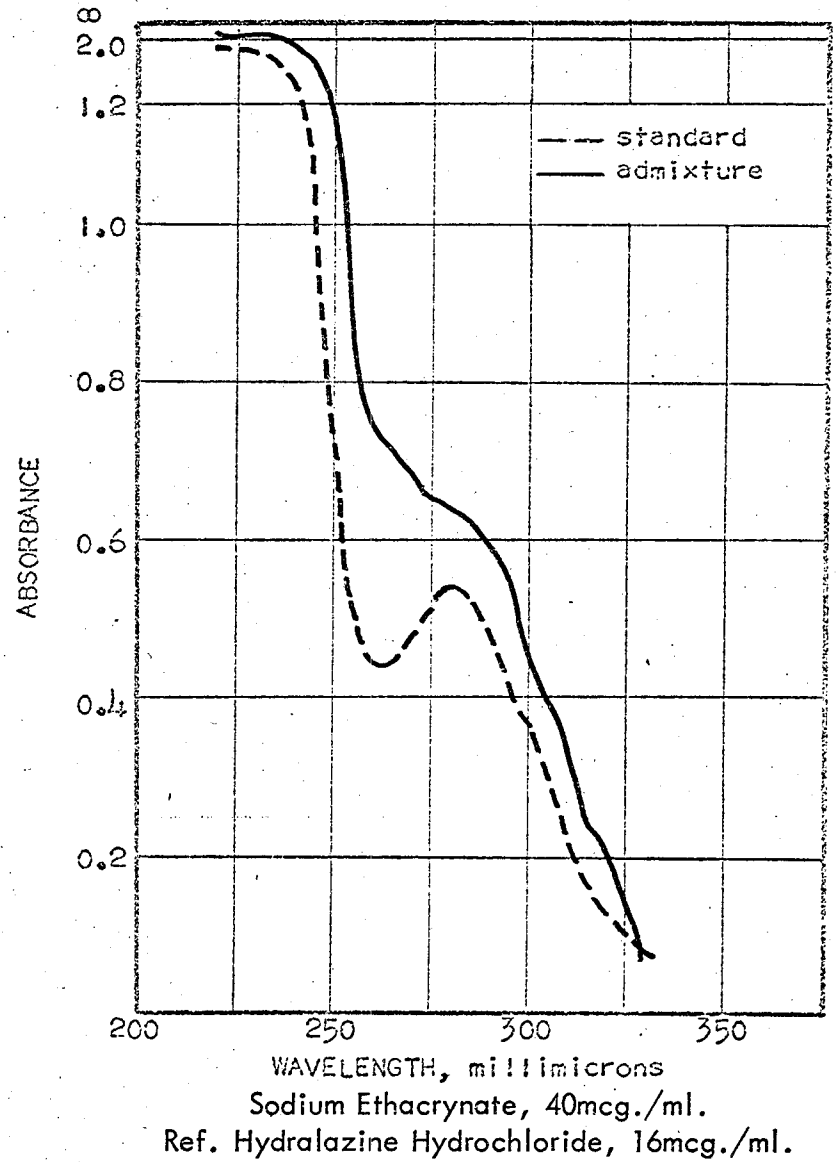



Graph 5

Standard Curve for Hydralazine Hydrochloride

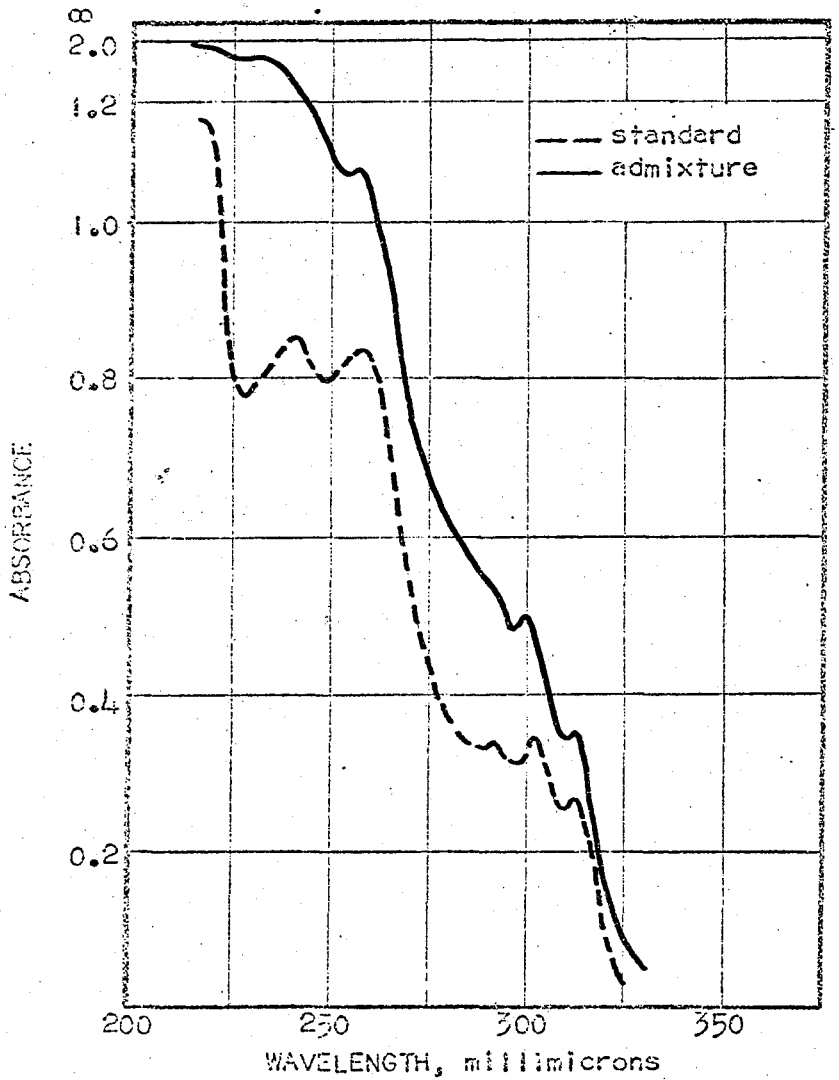



Hydralazine Hydrochloride, 16mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

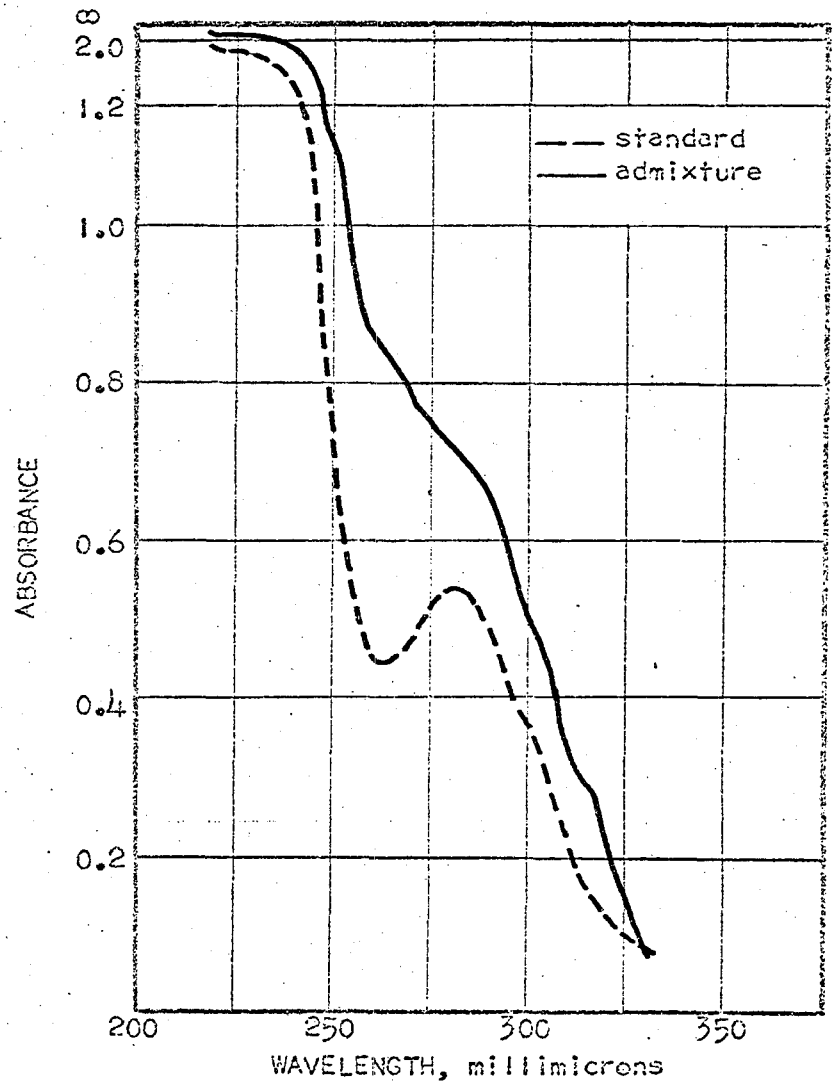



Sodium Ethacrynate, 40mcg./ml.
Ref. Hydralazine Hydrochloride, 16mcg./ml.

Fig. 10. U.V. Spectra of Admixture of Sodium Ethacrynate ( λ max 280)
. with Hydralazine Hydrochloride ( λ max 241) at 1 Hour.

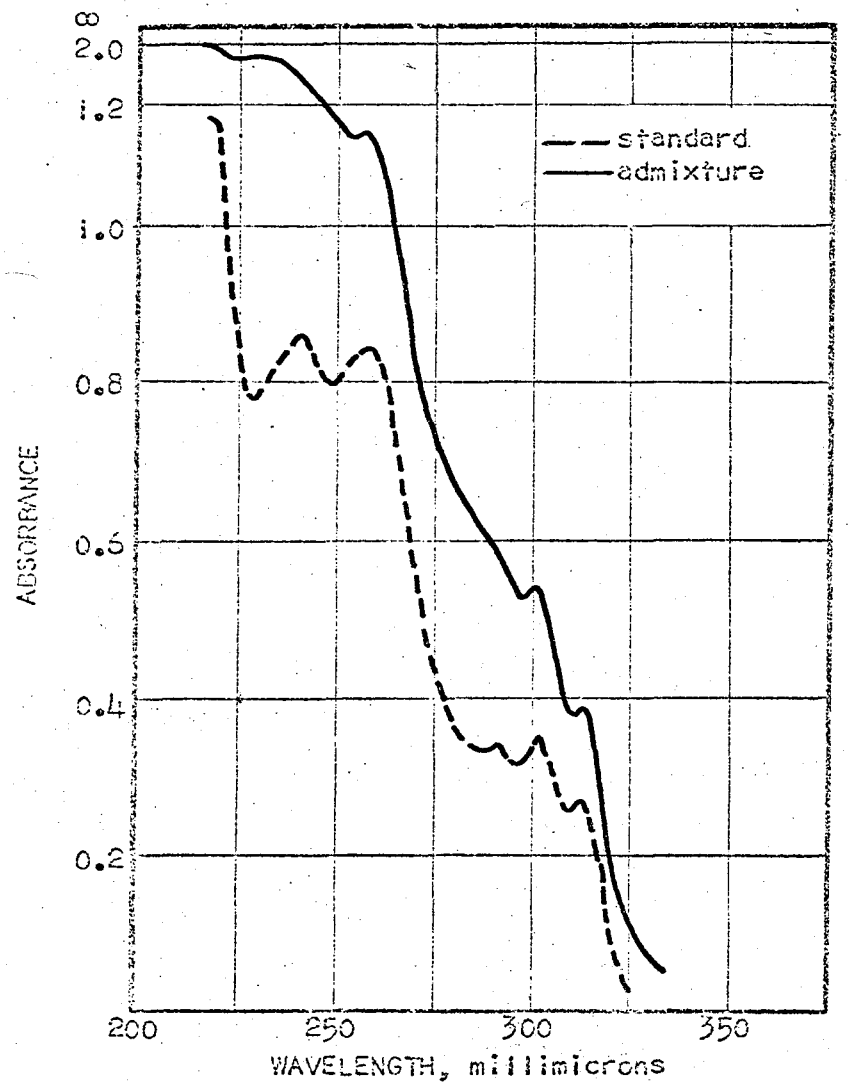



Hydralazine Hydrochloride, 16mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

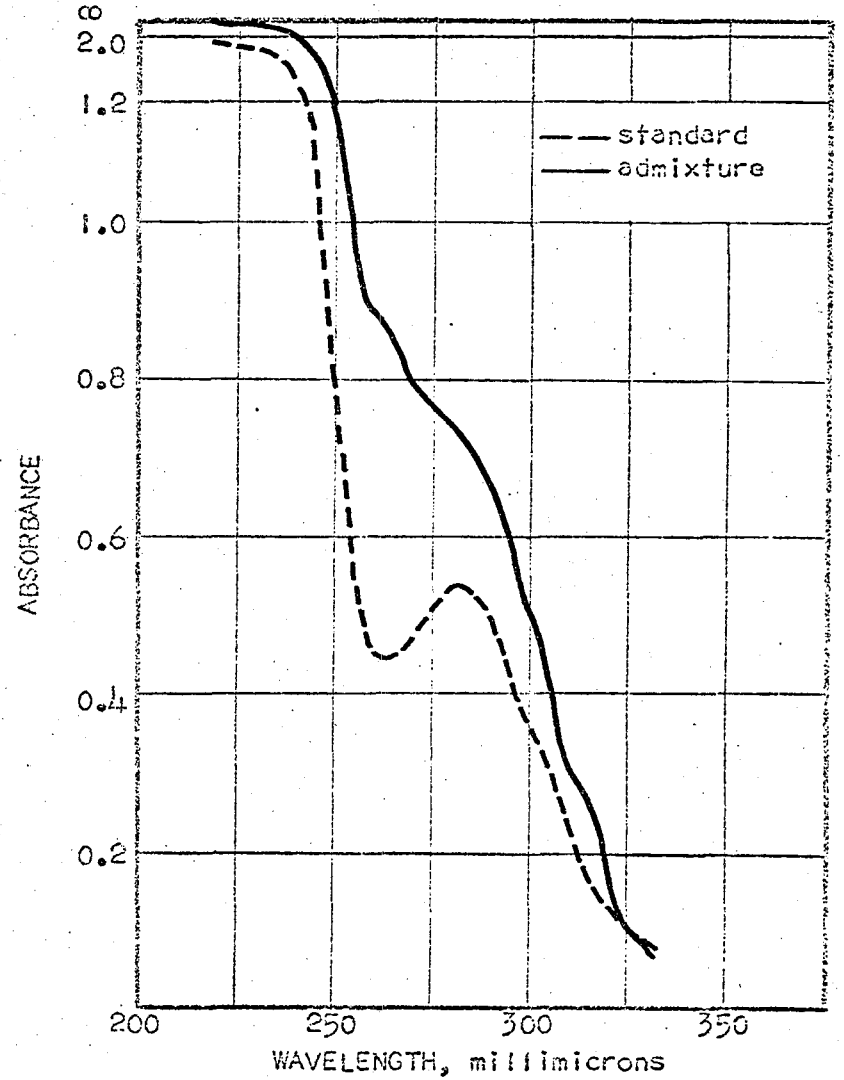



Sodium Ethacrynate, 40mcg./ml.
Ref. Hydralazine Hydrochloride, 16mcg./ml.

Fig. 11. U.V. Spectra of Admixture of Sodium Ethacrynate ($\lambda$ max 280) with Hydralazine Hydrochloride ($\lambda$ max 241) at 4 Hours.




Hydralazine Hydrochloride, 16mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.




Sodium Ethacrynate, 40mcg./ml.
Ref. Hydralazine Hydrochloride, 16mcg./ml.

Fig. 12. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$ max 280) with Hydralazine Hydrochloride ( $\lambda$ max 241) at 8 Hours.

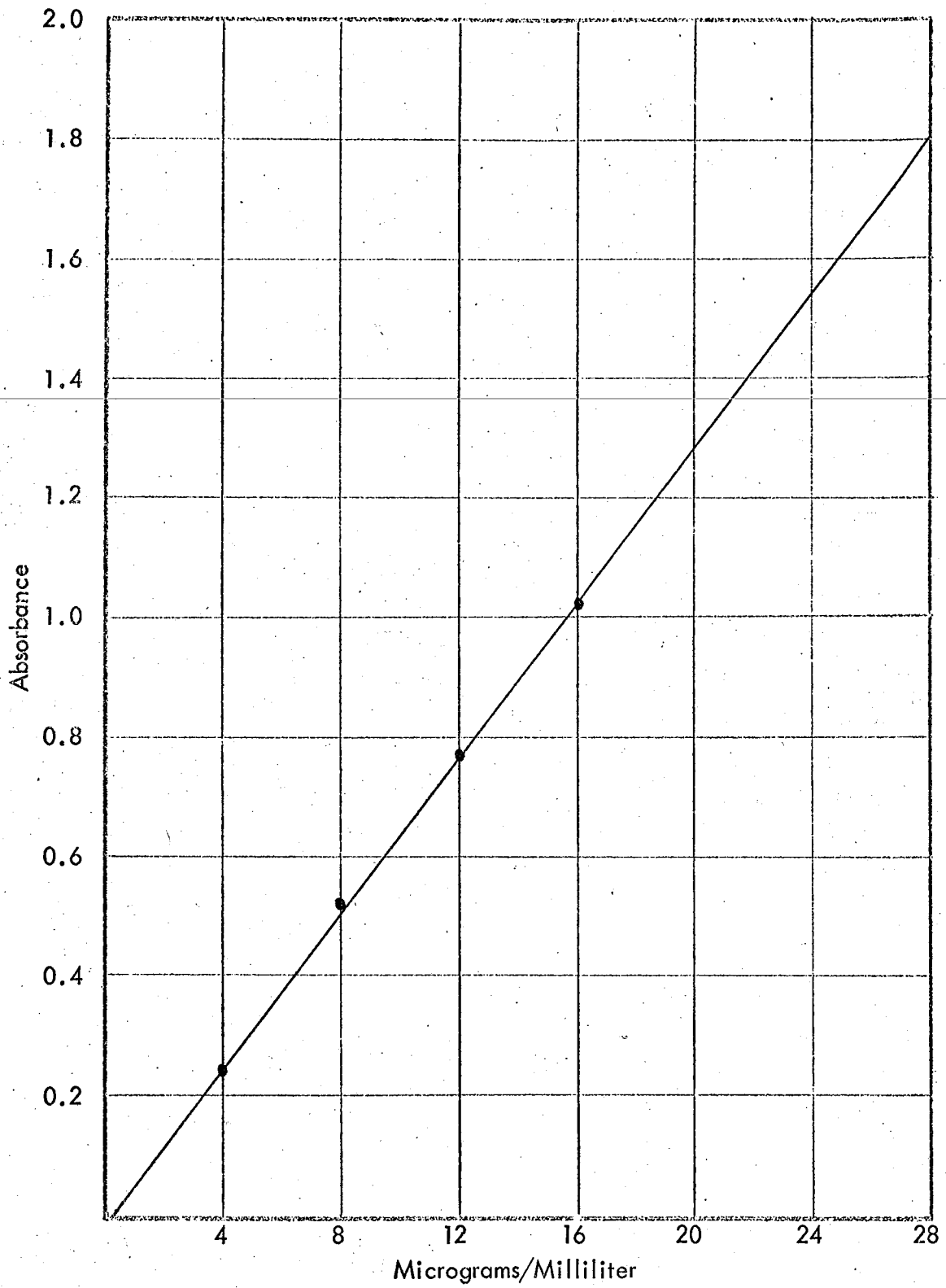
Procainamide Hydrochloride-Sodium Ethacrynate

The therapeutic concentration for sodium ethacrynate and procainamide hydrochloride are 50mcg./ml. and 1000mcg./ml., respectively. The capabilities of the spectrophotometer prevented the use of this concentration for the procainamide hydrochloride determination, and therefore, appropriate dilutions were made to achieve an optimum concentration of 8mcg./ml. The spectrum showed a decrease in the absorbance at the $\lambda$max for sodium ethacrynate (See Fig. 13-15), and some loss in the absorbance was also noted for the spectrum of procainamide hydrochloride. The decrease indicates a loss in concentration and is suggestive of a chemical interaction. On the other hand, direct undiluted admixture of two drops of each parenteral product resulted in a clear solution, suggestive of an absence of physical interaction. The results of the pH determination are listed in Table V.

TABLE V

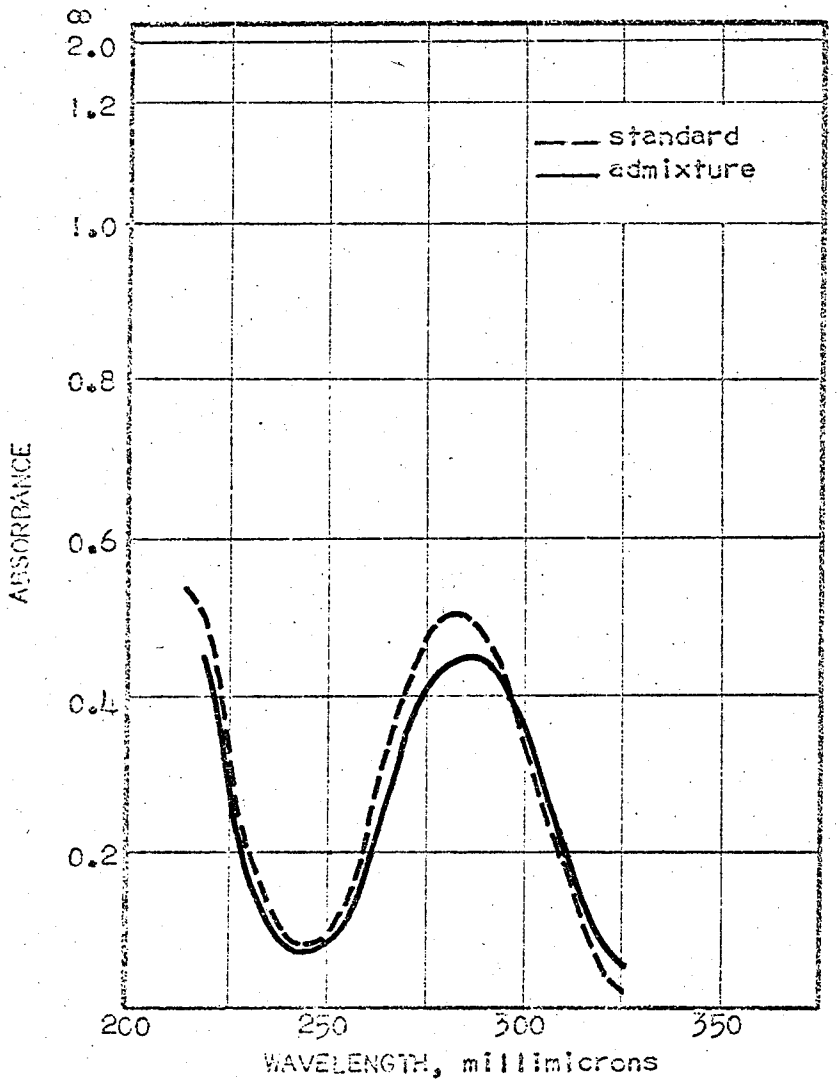
Change in pH of Procainamide Hydrochloride-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Procainamide Hydrochloride, 1000mcg./ml. | 5.3 | 5.2 | 5.0 |
| Therapeutic Admixture | 5.8 | 6.1 | 5.8 |
| Dilution | 5.8 | 5.9 | 5.9 |

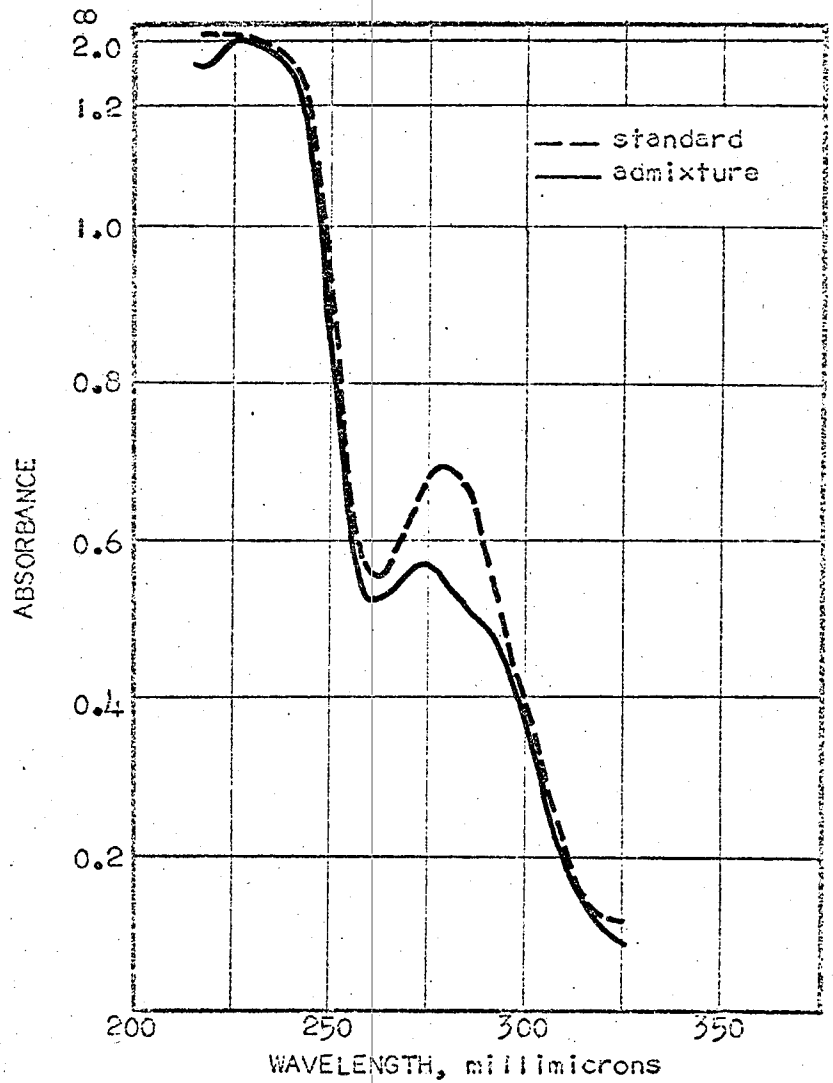



Graph 6

Standard Curve for Procainamide Hydrochloride

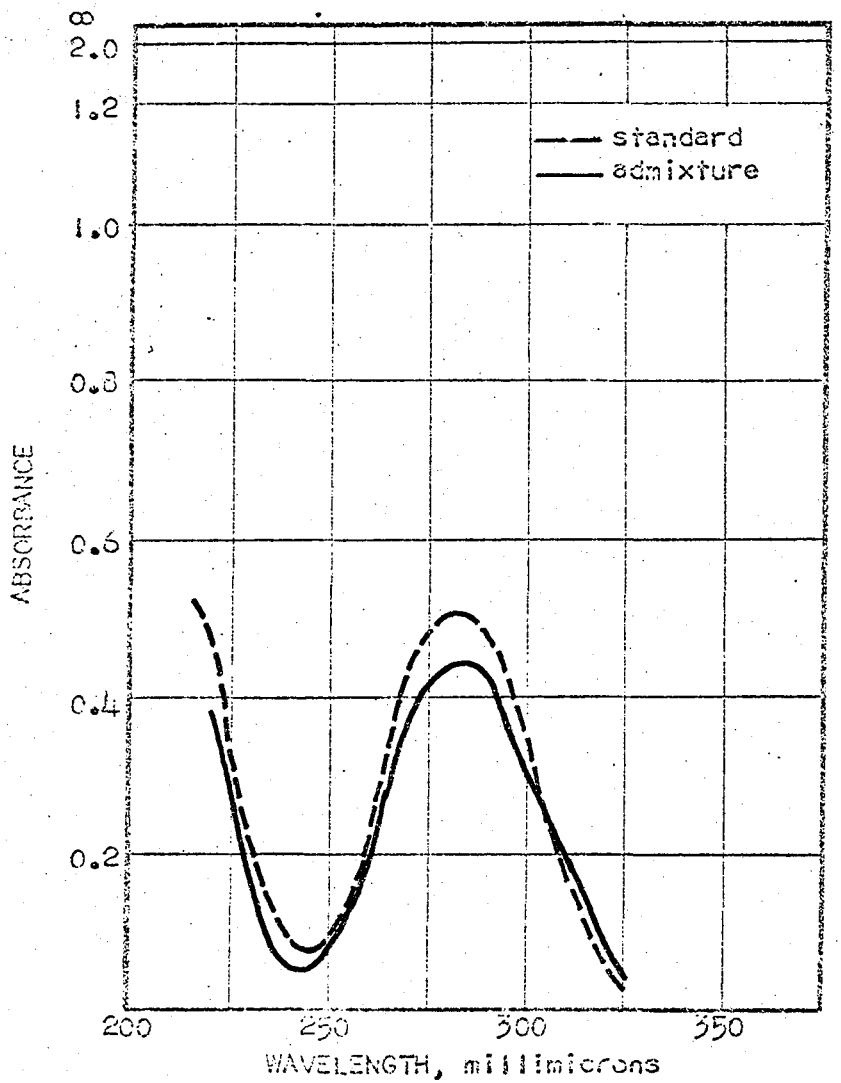



Procainamide Hydrochloride, 8mcg./ml.
Ref. Sodium Ethacrynate, 0.4mcg./ml.

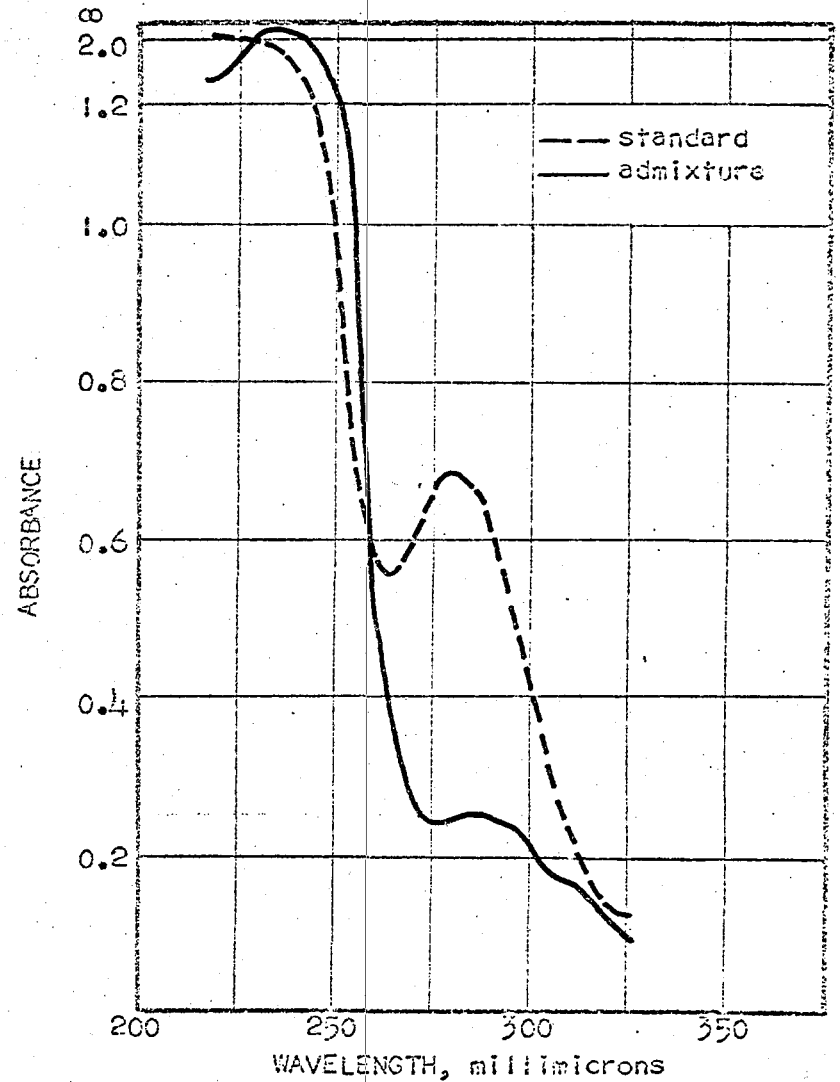



Sodium Ethacrynate, 50mcg./ml.
Ref. Procainamide Hydrochloride, 40mcg./ml.

Fig. 13. U.V. Spectra of Admixture of Sodium Ethacrynate ( λmax 280) with Procainamide Hydrochloride ( λ max 280) at 1 Hour.

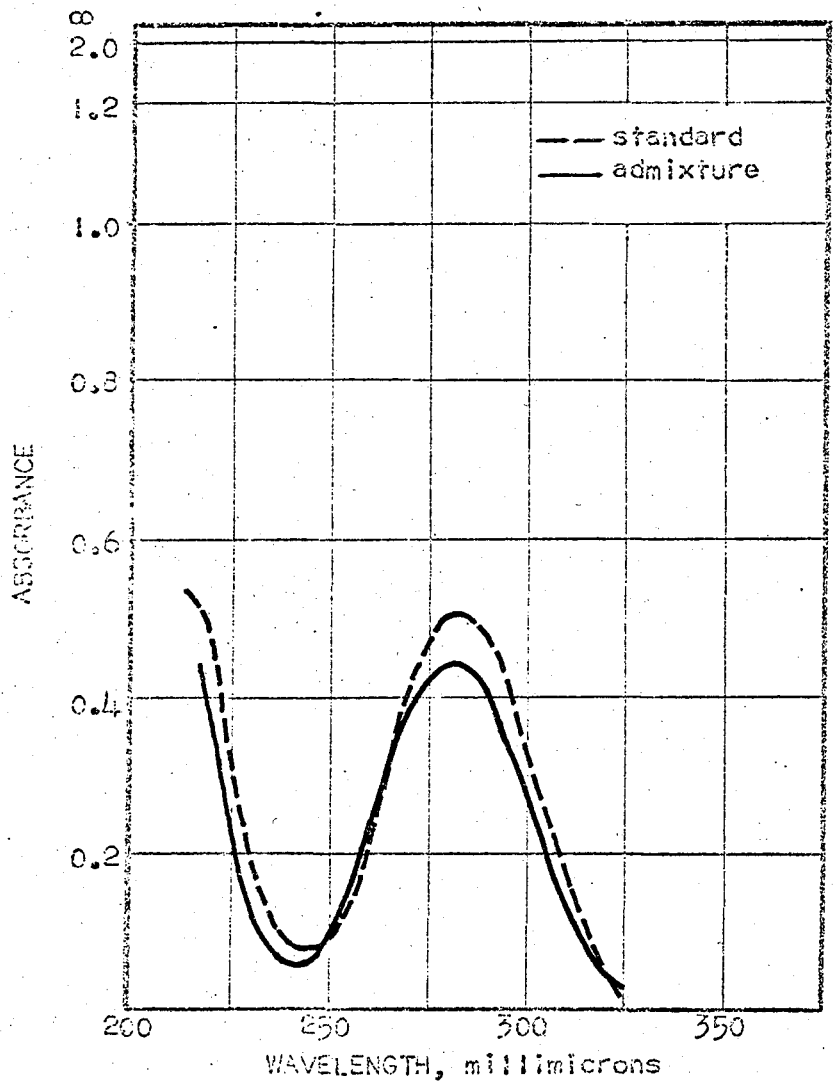



Procainamide Hydrochloride, 8mcg./ml.
Ref. Sodium Ethacrynate, 0.4mcg./ml.

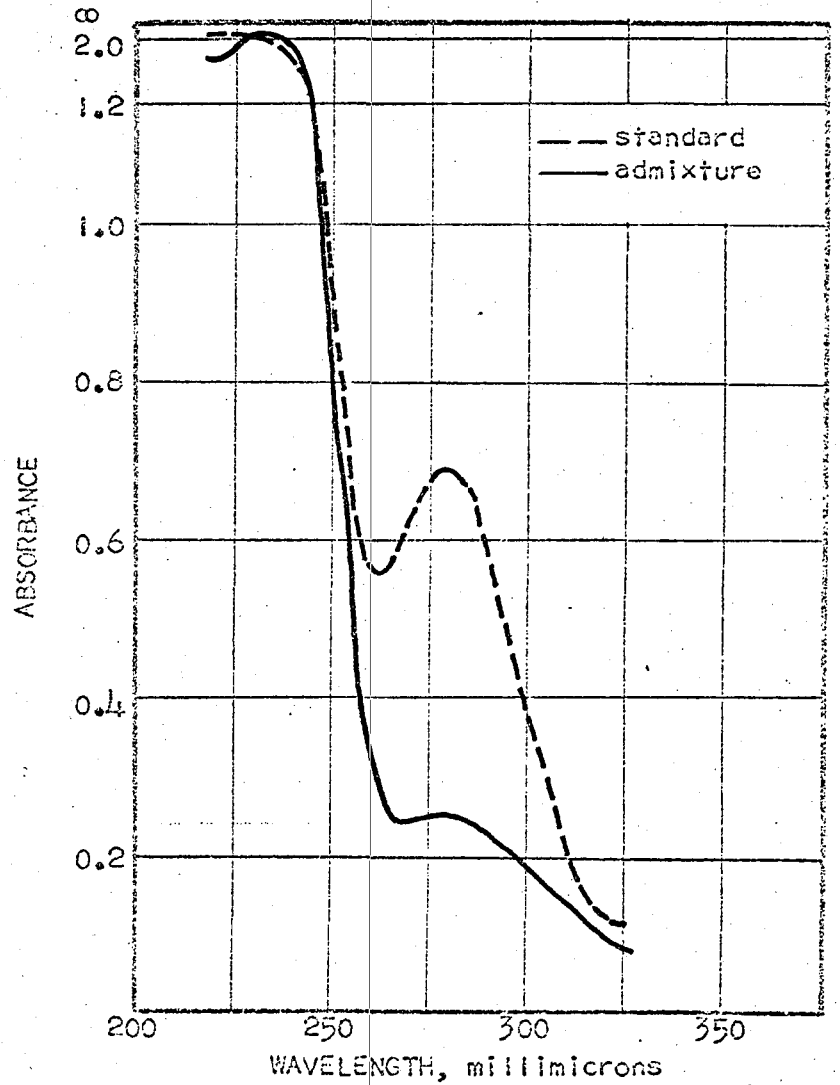



Sodium Ethacrynate, 50mcg./ml.
Ref. Procainamide Hydrochloride, 40mcg./ml.

Fig. 14. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$ max 280) with Procainamide Hydrochloride ( $\lambda$ max 280) at 4 Hours.




Procainamide Hydrochloride, 8mcg./ml.
Ref. Sodium Ethacrynate, 0.4mcg./ml.




Sodium Ethacrynate, 50mcg./ml.
Ref. Procainamide Hydrochloride, 40mcg./ml.

Fig. 15. U.V. Spectra of Admixture of Sodium Ethacrynate ( λ max 280) with Procainamide Hydrochloride ( λ max 280) at 8 Hours.

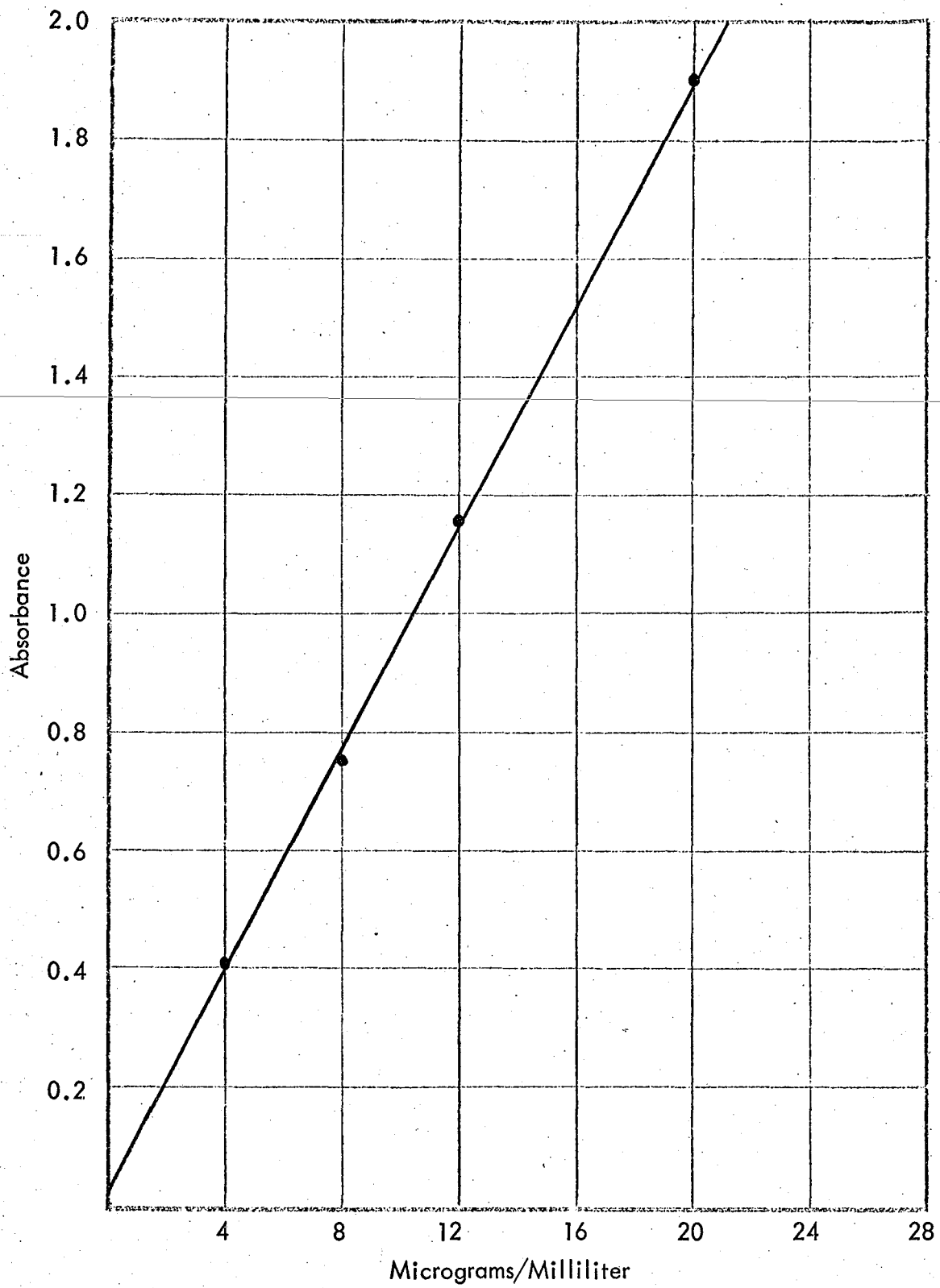
Prochlorperazine Edisylate-Sodium Ethacrynate

Sodium ethacrynate and prochlorperazine edisylate were mixed in therapeutic concentration, 80mcg./ml., and 20mcg./ml., respectively. Appropriate dilutions were performed to achieve the optimum concentration of sodium ethacrynate, 40mcg./ml., and prochlorperazine edisylate, 10mcg./ml. The absorption spectrum obtained for each drug in the admixture duplicated the reference spectrum expected (See Fig. 16-18). Some loss in absorbance was detected, but the loss was not significant and no appreciable loss in concentration occurred. Undiluted admixture of these two drugs resulted in a cloudy solution, indicative of a physical incompatibility, while admixture at therapeutic concentration produced no visible change in the solution and therefore, no physical incompatibility can be reported. The results of the pH determination are listed in Table VI.

TABLE VI

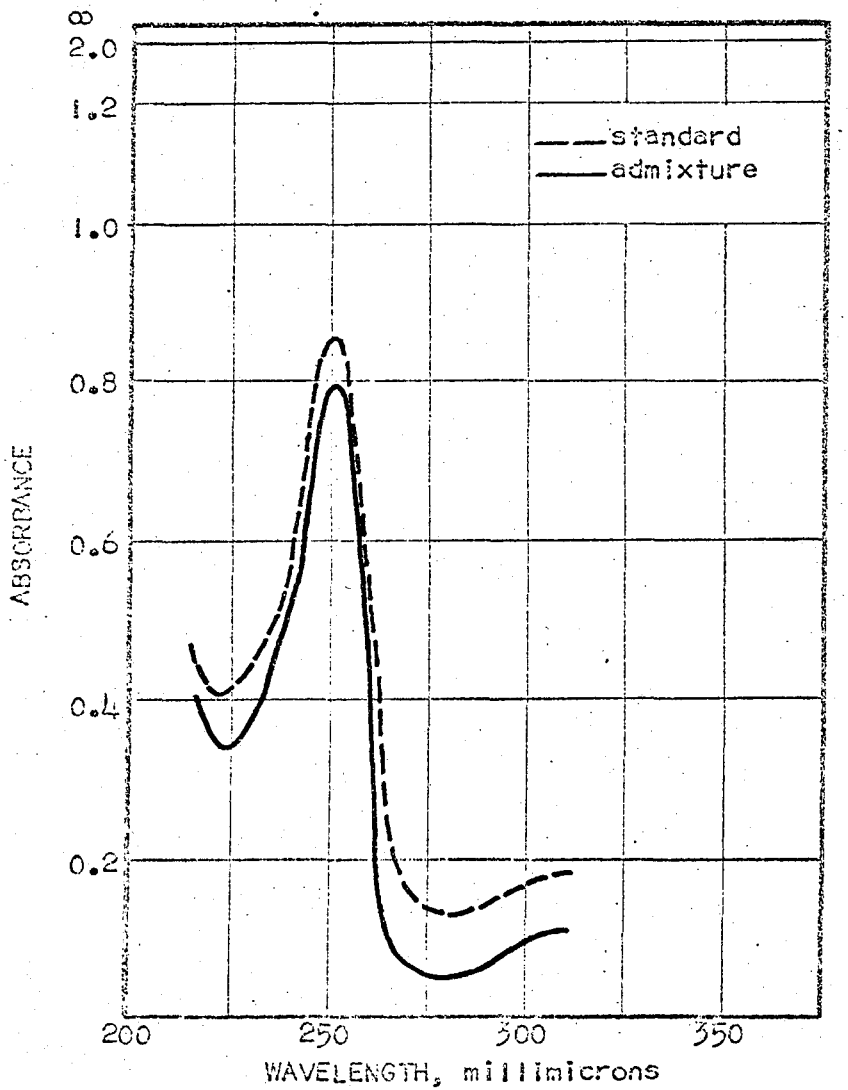
Change in pH of Prochlorperazine Edisylate-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Prochlorperazine Edisylate, 20mcg./ml. | 6.0 | 5.7 | 5.7 |
| Therapeutic Admixture | 6.3 | 6.3 | 6.3 |
| Dilution | 6.5 | 6.4 | 6.6 |

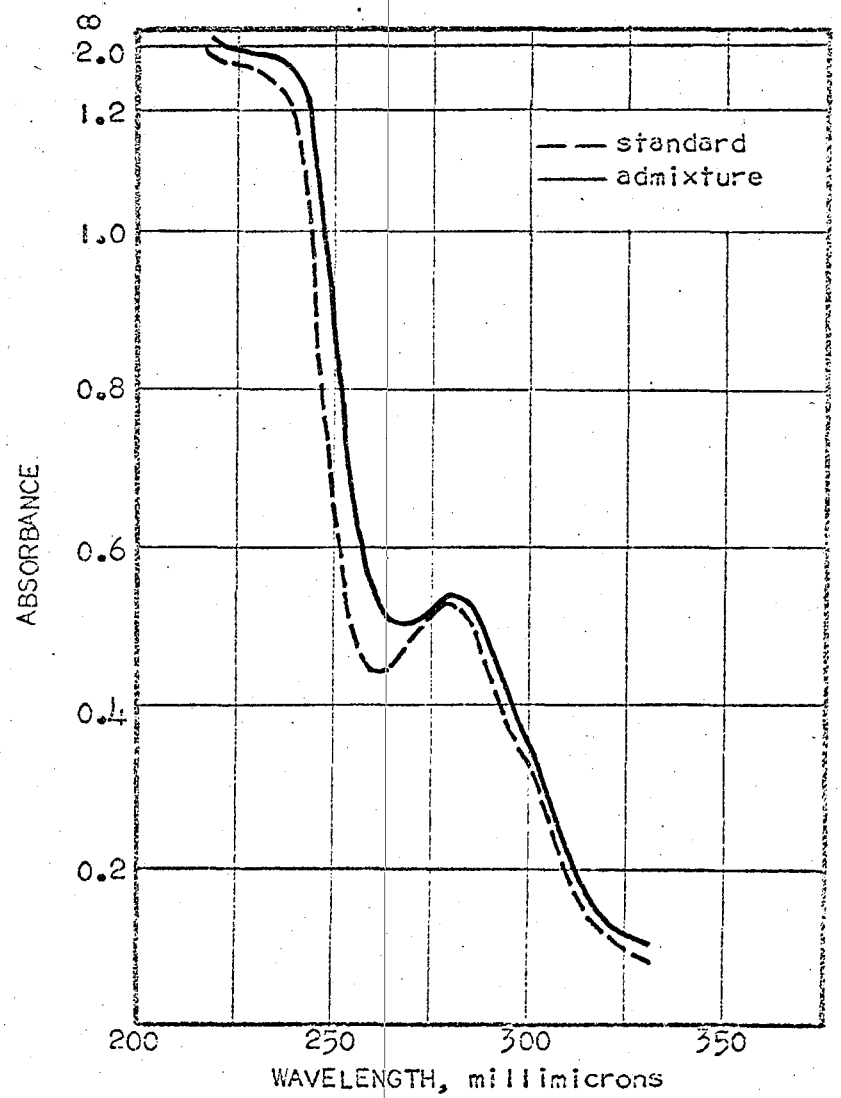



Graph 7

Standard Curve for Prochlorperazine Edisylate

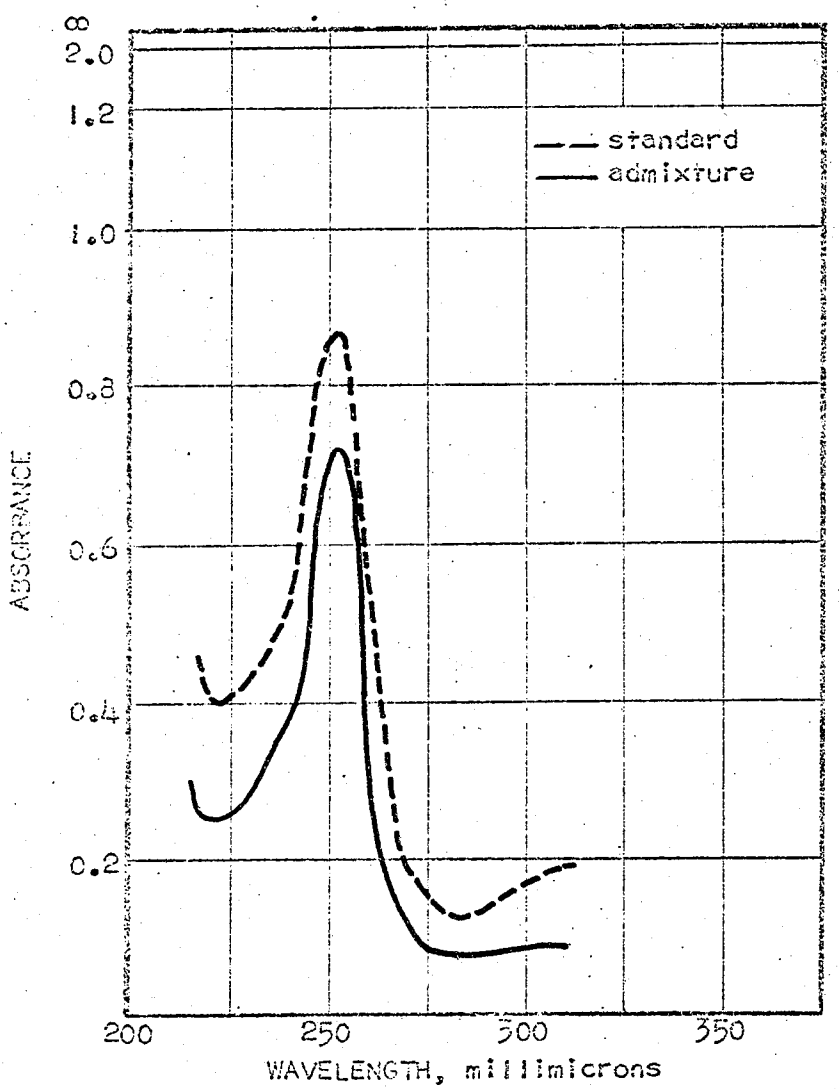



Prochlorperazine Edisylate, 10mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

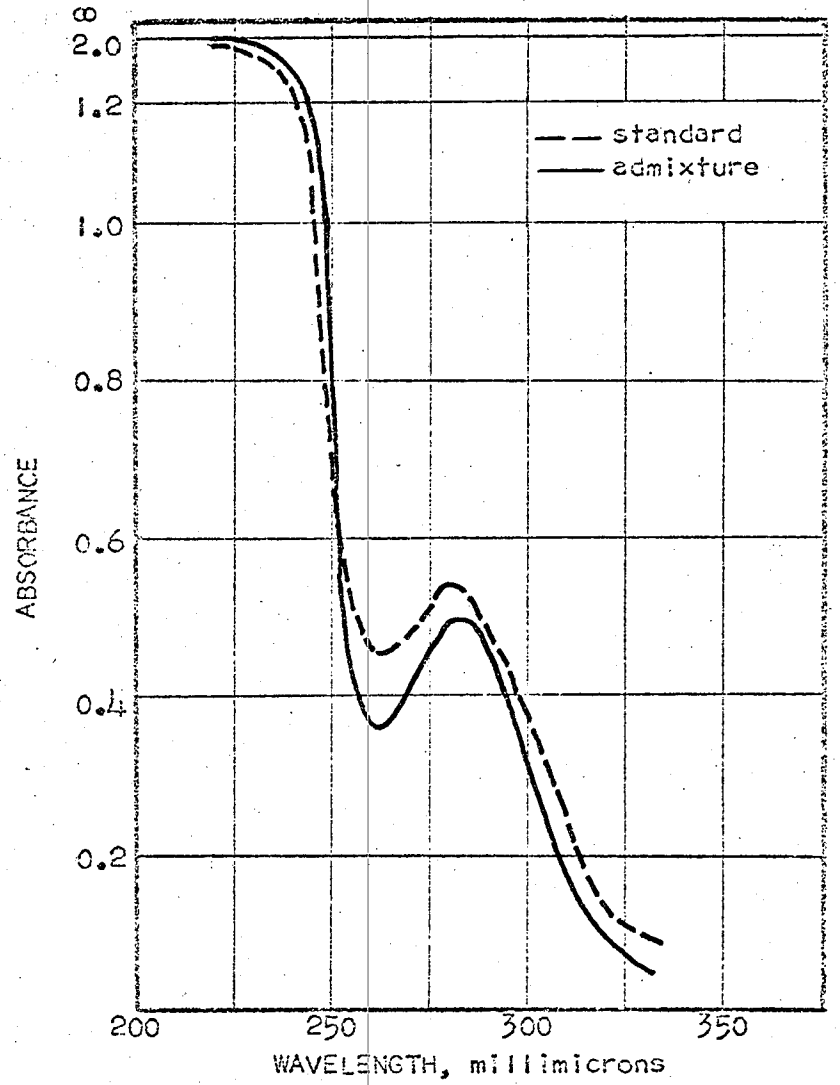



Sodium Ethacrynate, 40mcg./ml.
Ref. Prochlorperazine Edisylate, 10mcg./ml.

Fig. 16. U.V. Spectra of Admixture of Sodium Ethacrynate ($\lambda$max 280) with Prochlorperazine Edisylate ($\lambda$max 256) at 1 Hour.

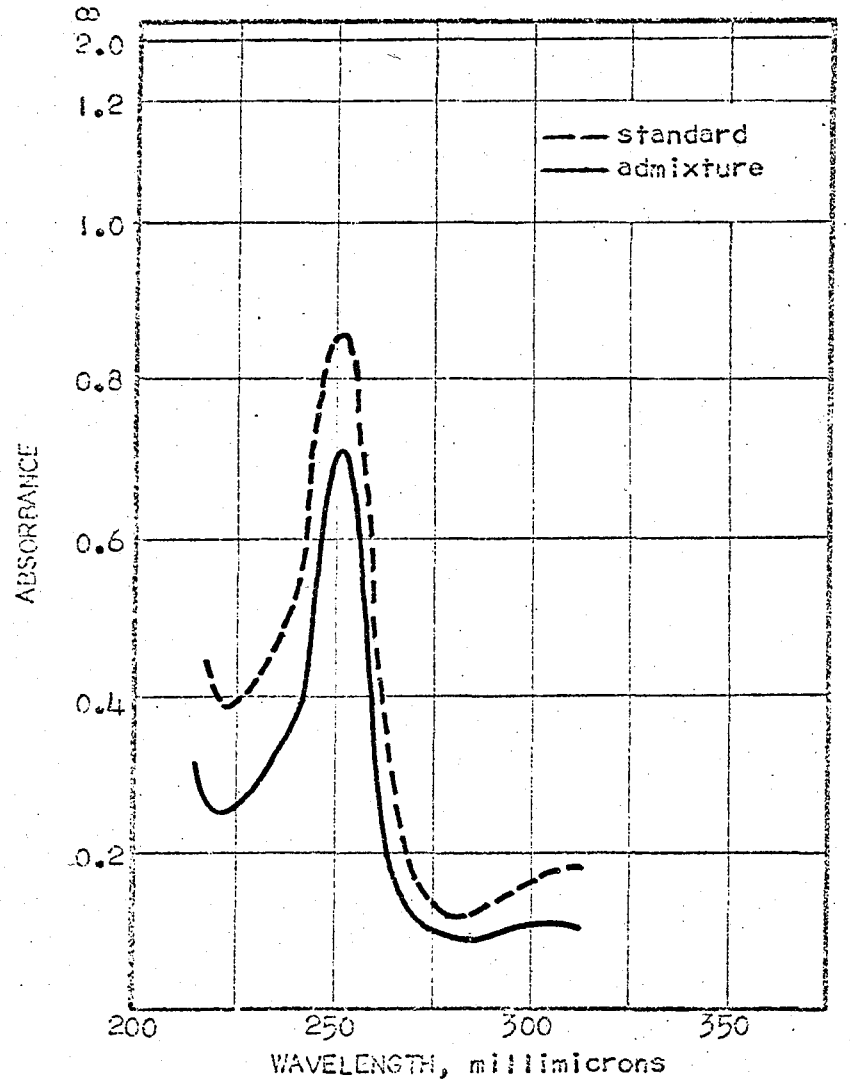



Prochlorperazine Edisylate, 10mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.

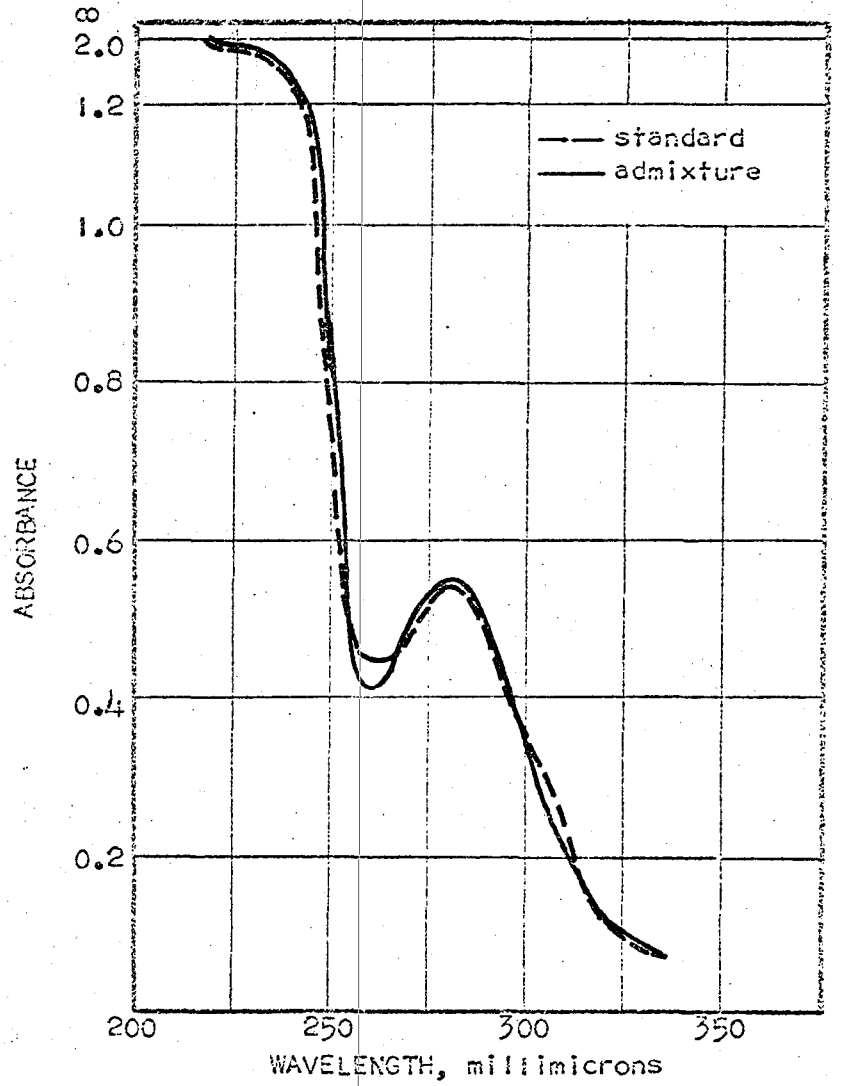



Sodium Ethacrynate, 40mcg./ml.
Ref. Prochlorperazine Edisylate, 10mcg./ml.

Fig. 17. U.V. Spectra of Admixture of Sodium Ethacrynate (λ max 280) with Prochlorperazine Edisylate (λ max 256) at 4 Hours.




Prochlorperazine Edisylate, 10mcg./ml.
Ref. Sodium Ethacrynate, 40mcg./ml.




Sodium Ethacrynate, 40mcg./ml.
Ref. Prochlorperazine Edisylate, 10mcg./ml.

Fig. 18. U.V. Spectra of Admixture of Sodium Ethacrynate (λ max 280) with Prochlorperazine Edisylate (λ max 256) at 8 Hours.

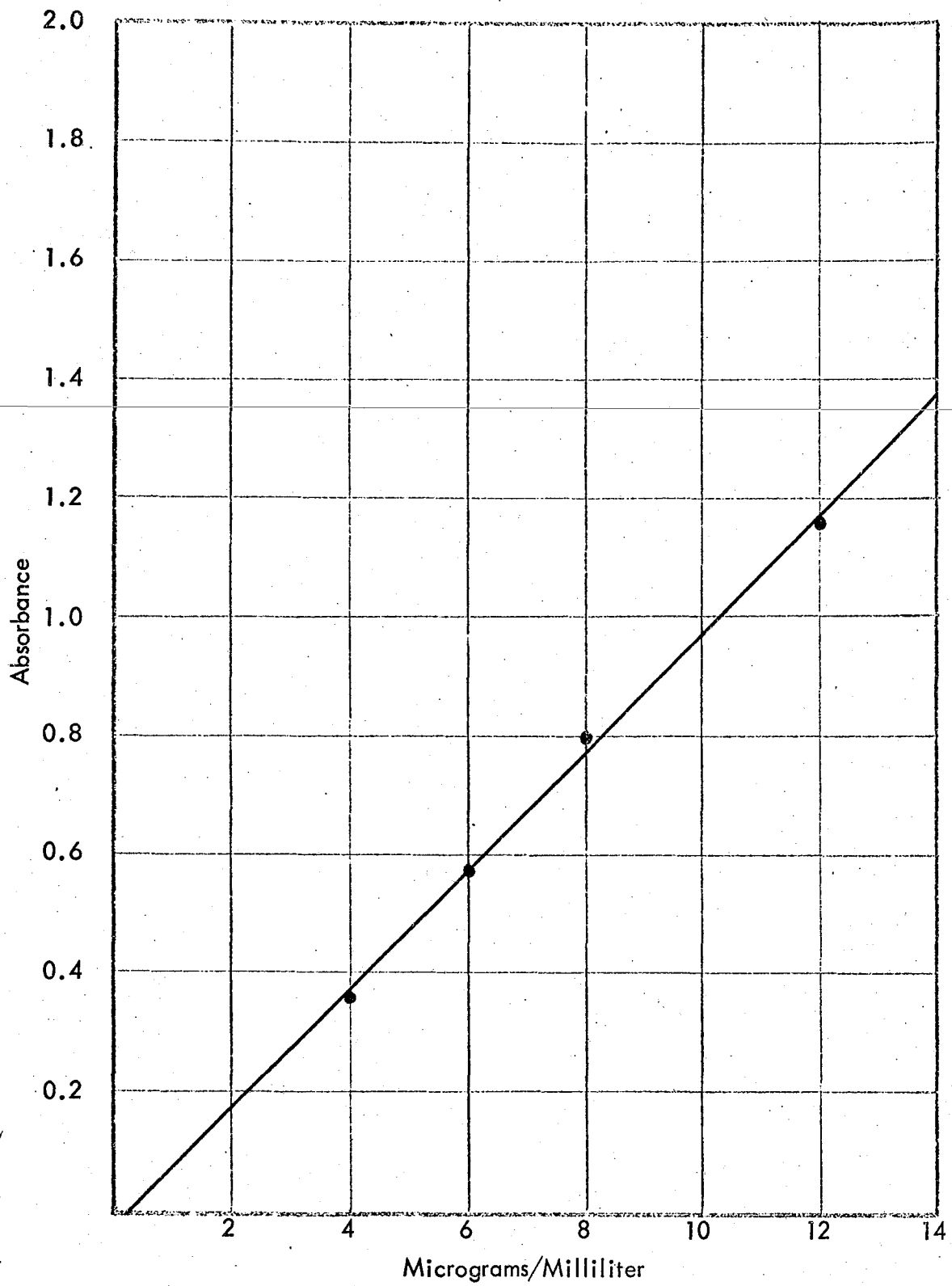
Promazine Hydrochloride-Sodium Ethacrynate

The therapeutic concentrations of sodium ethacrynate, 50mcg./ml., and promazine hydrochloride, 50mcg./ml., were appropriately diluted to obtain a concentration of 40mcg./ml., and 8mcg./ml., respectively. The absorption spectrum of each was not altered to any significant extent, but some loss in the absorbance at the λmax did occur (See Fig. 19-21). This loss in absorbance was not significant and therefore, may suggest the absence of a chemical interaction. No particulate matter was observed in the admixture at therapeutic concentrations, but direct, undiluted admixture resulted in the formation of a cloudy solution. The results of the pH determination are listed in Table VII.

TABLE VII

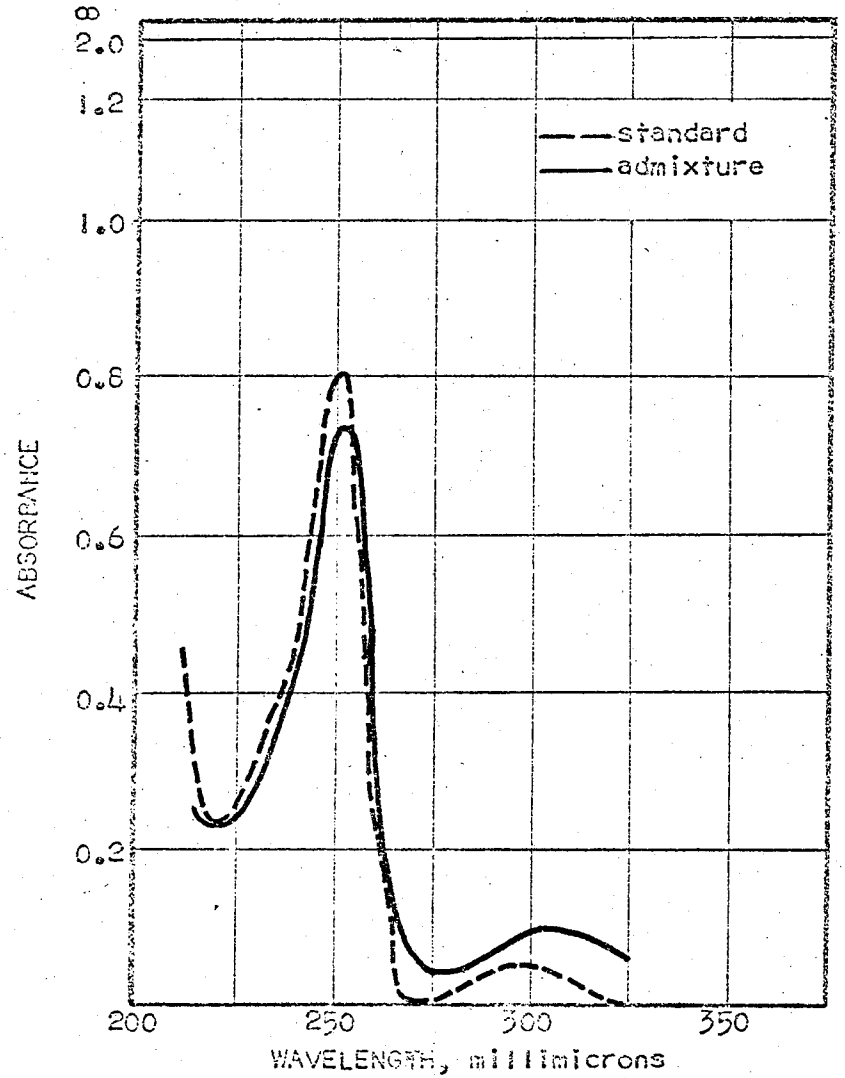
Change in pH of Prochlorperazine Edisylate-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Promazine Hydrochloride, 50mcg./ml. | 6.2 | 6.4 | 6.5 |
| Therapeutic Admixture | 6.4 | 6.3 | 6.2 |
| Dilution | 6.7 | 6.3 | 6.4 |

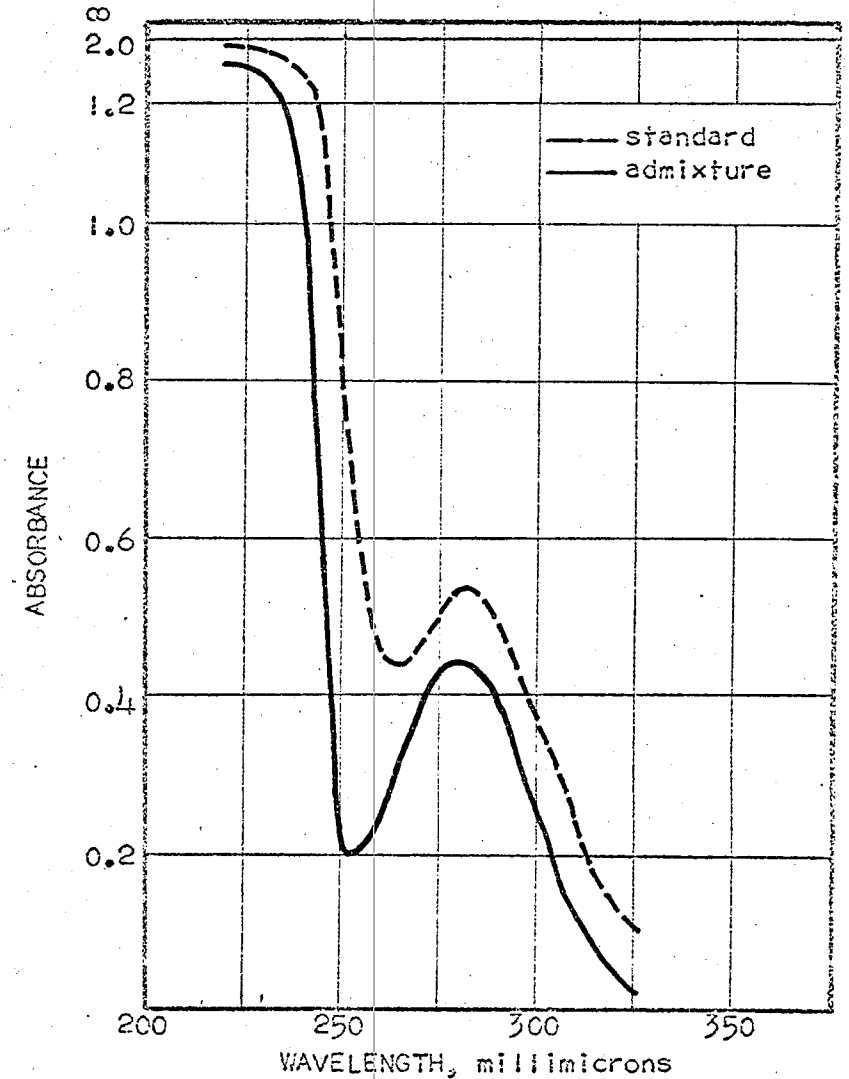



Graph 8

Standard Curve for Promazine Hydrochloride

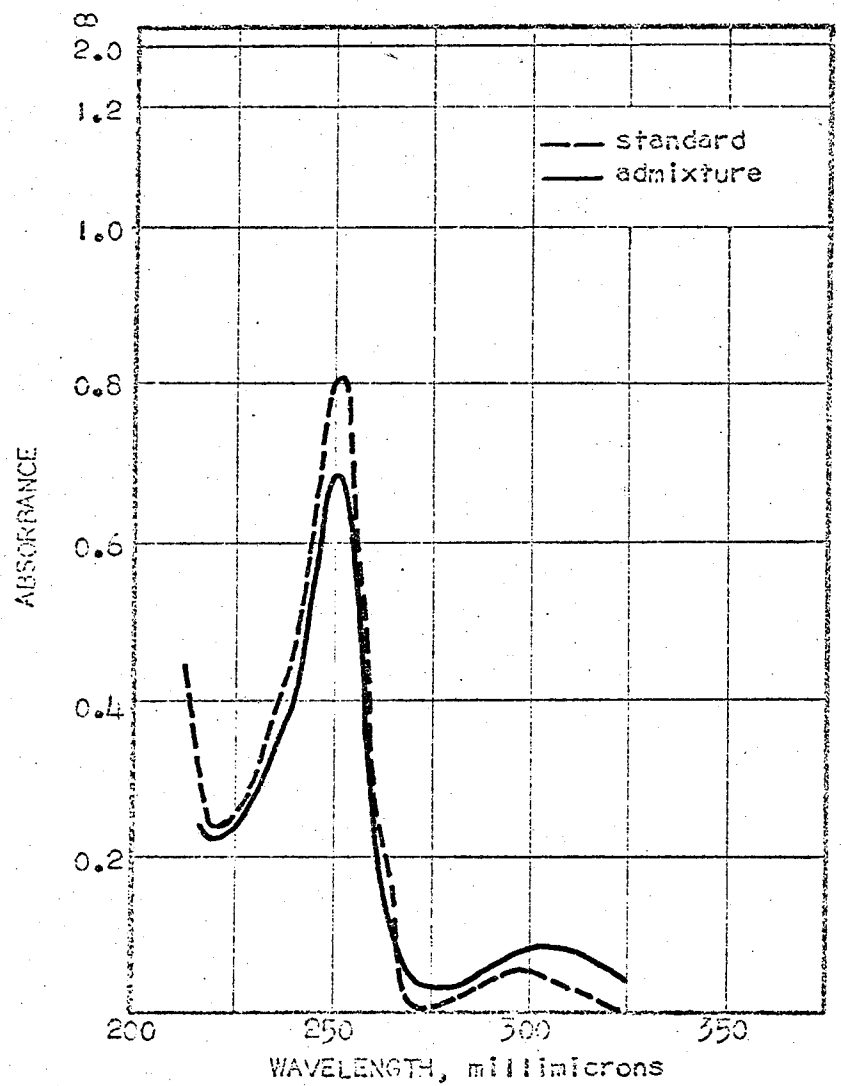



Promazine Hydrochloride, 8mcg./ml.
Ref. Sodium Ethacrynate, 8mcg./ml.

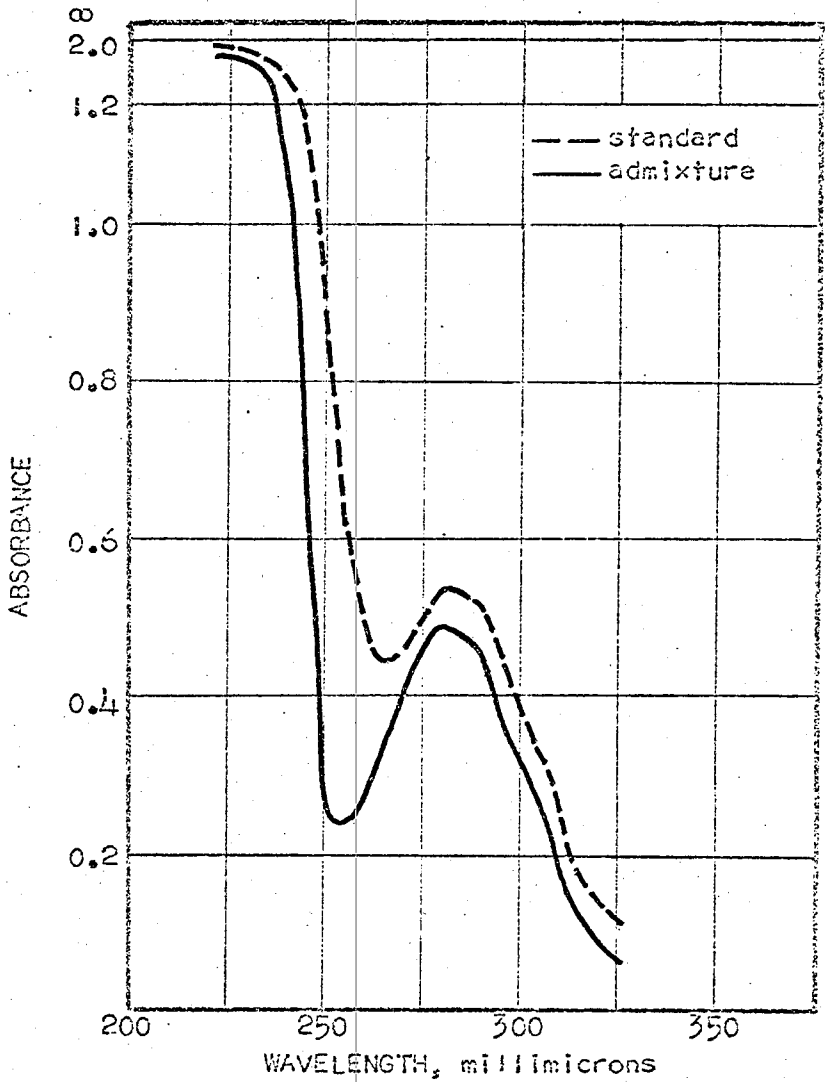



Sodium Ethacrynate, 40mcg./ml.
Ref. Promazine Hydrochloride, 40mcg./ml.

Fig. 19. U.V. Spectra of Admixture of Sodium Ethacrynate ( $\lambda$max 280) with Promazine Hydrochloride ( $\lambda$ max 253) at 1 Hour.

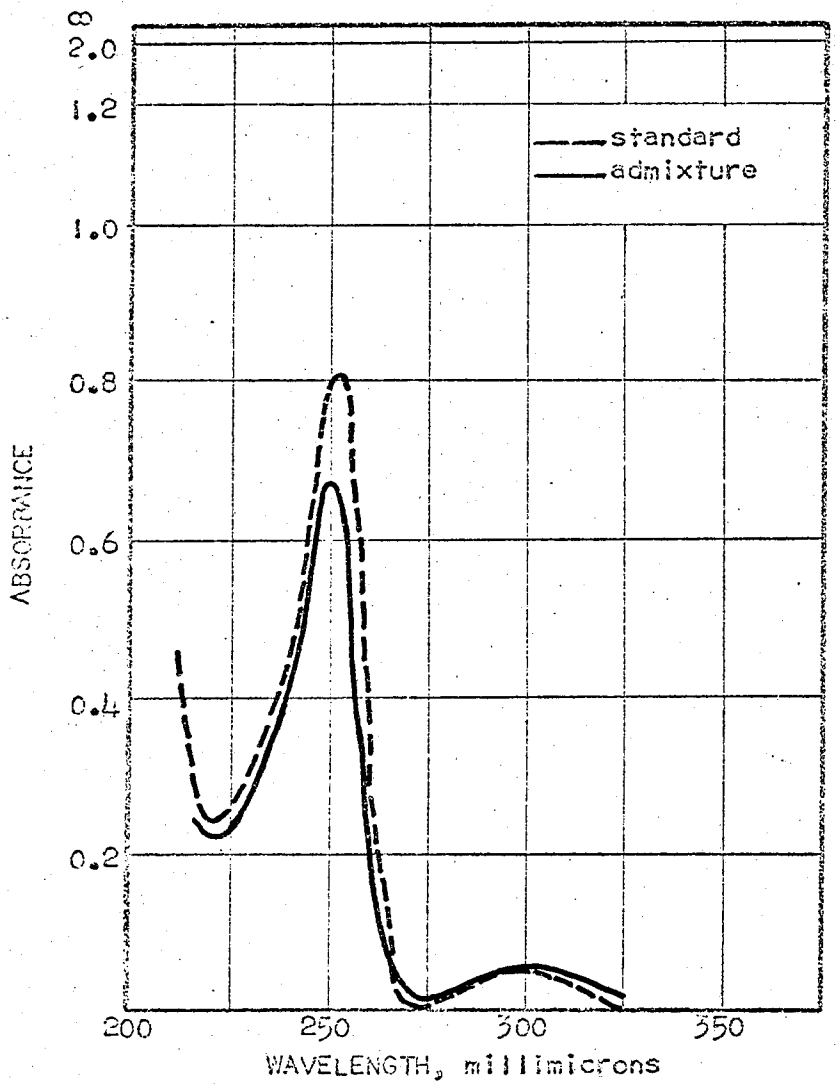



Promazine Hydrochloride, 8mcg./ml.
Ref. Sodium Ethacrynate, 8mcg./ml.

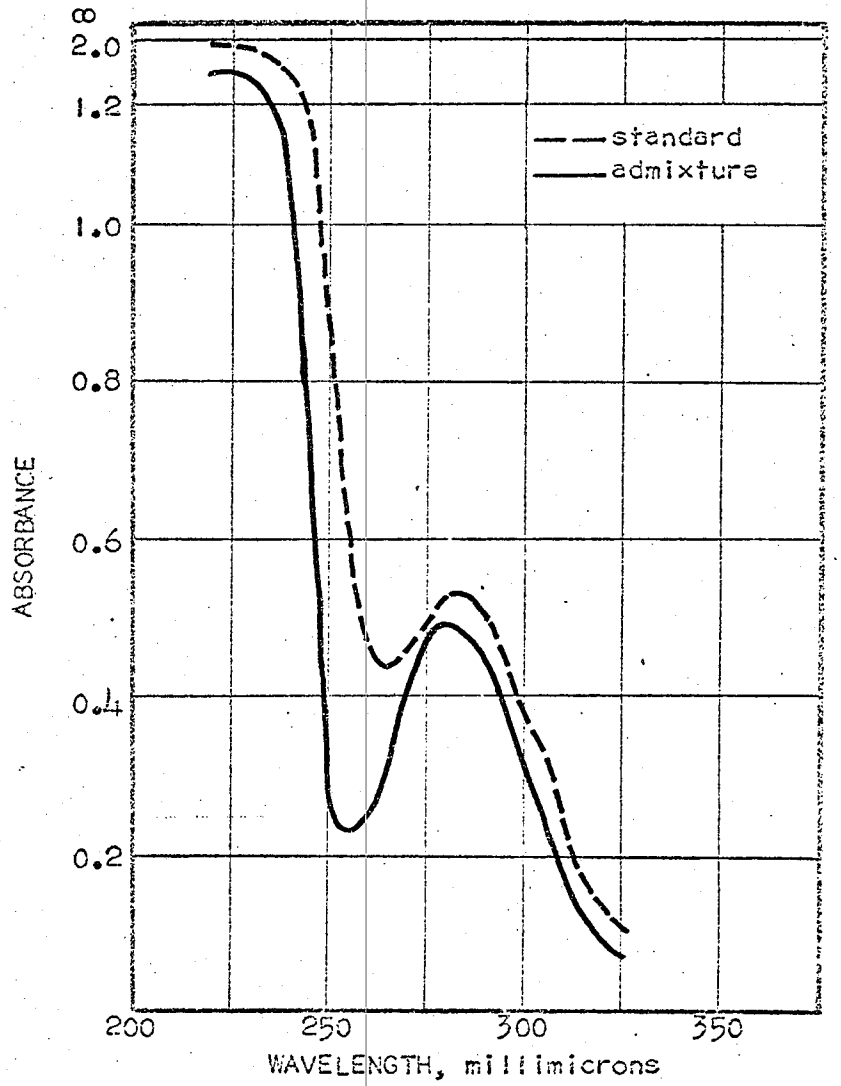



Sodium Ethacrynate, 40mcg./ml.
Ref. Promazine Hydrochloride, 40mcg./ml.

Fig. 20. U.V. Spectra of Admixture of Sodium Ethacrynate ( λ max 280) with Promazine Hydrochloride ( λ max 253) at 4 Hours.




Promazine Hydrochloride, 8mcg./ml.
Ref. Sodium Ethacrynate, 8mcg./ml.




Sodium Ethacrynate, 40mcg./ml.
Ref. Promazine Hydrochloride, 40mcg./ml.

Fig. 21. U.V. Spectra of Admixture of Sodium Ethacrynate ($\lambda$ max 280) with Promazine Hydrochloride ($\lambda$ max 253) at 8 Hours.

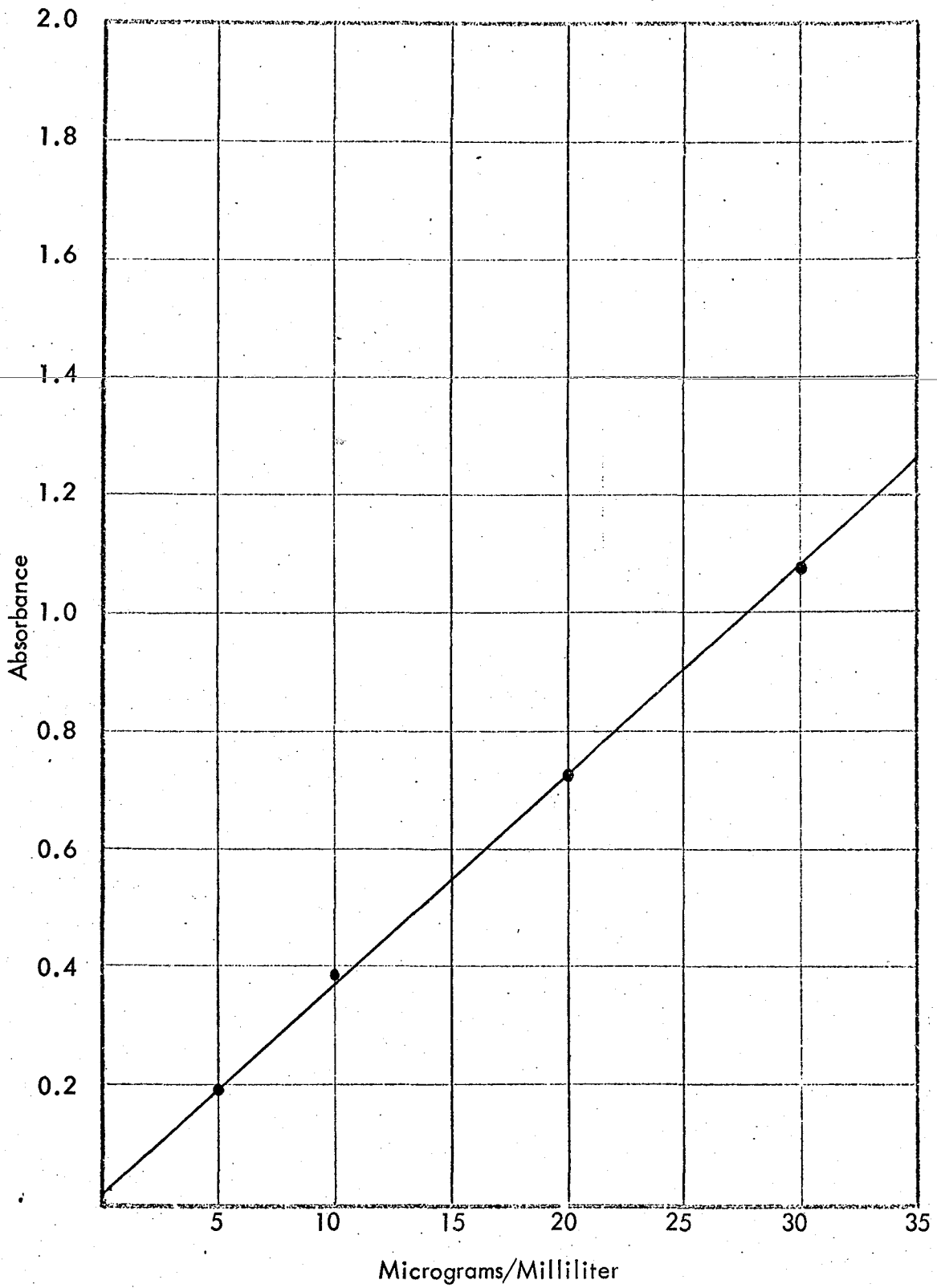
Reserpine-Sodium Ethacrynate

An admixture was prepared using 50mcg./ml. of sodium ethacrynate and 20mcg./ml. of reserpine. The solution turned cloudy, indicative of physical evidence of a chemical reaction. Undiluted admixture of each drug also produced a cloudy solution. This particulate matter prevented the use of spectrophotometric measurements to determine the effect of this interaction on the absorption spectra. The results of the pH determination are listed in Table VIII.

TABLE VIII

Change in pH of Reserpine-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Reserpine, 5mcg./ml. | 4.2 | 4.2 | 4.0 |
| Therapeutic Admixture Dilution | 4.0 | 4.0 | 4.0 |




Graph 9

Standard Curve for Reserpine

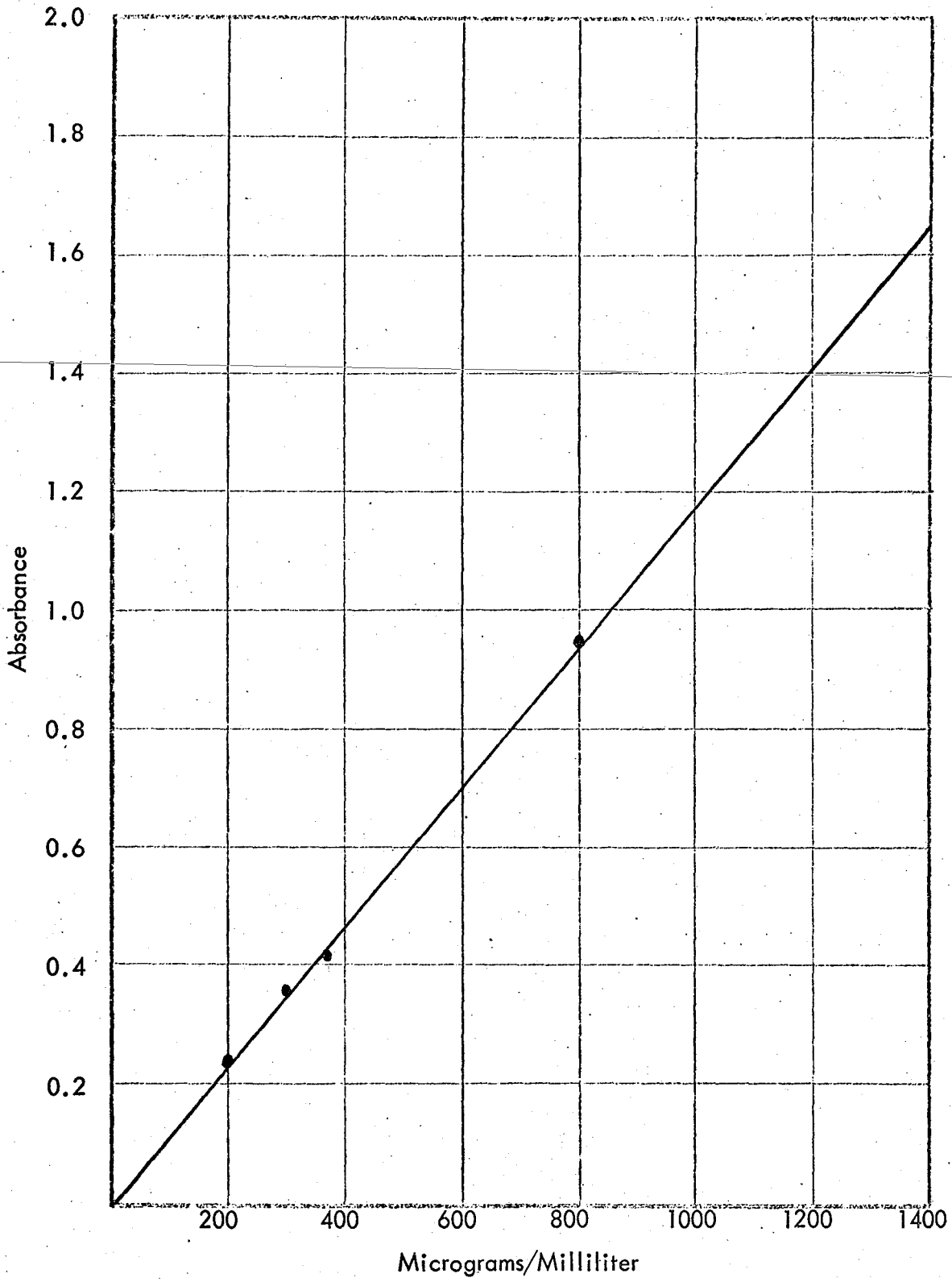
Tolazoline Hydrochloride-Sodium Ethacrynate

A clear solution resulted when sodium ethacrynate and tolazoline hydrochloride were mixed undiluted on a microscope slide. This observation would indicate a physical compatibility. Sodium ethacrynate was used in therapeutic concentration, 50mcg./ml., while that of tolazoline hydrochloride was the optimum concentration of 400mcg./ml. This admixture also resulted in a clear solution. The absorption spectrum of each of these drugs in the admixture was altered and the presence of secondary peaks was evident (See Fig. 22-24). This is indicative of a change in the chemical nature of the admixture. However, it must be noted that tolazoline hydrochloride was present in a concentration that is eight times the therapeutic concentration. The results of the pH determination are listed in Table IX.

TABLE IX

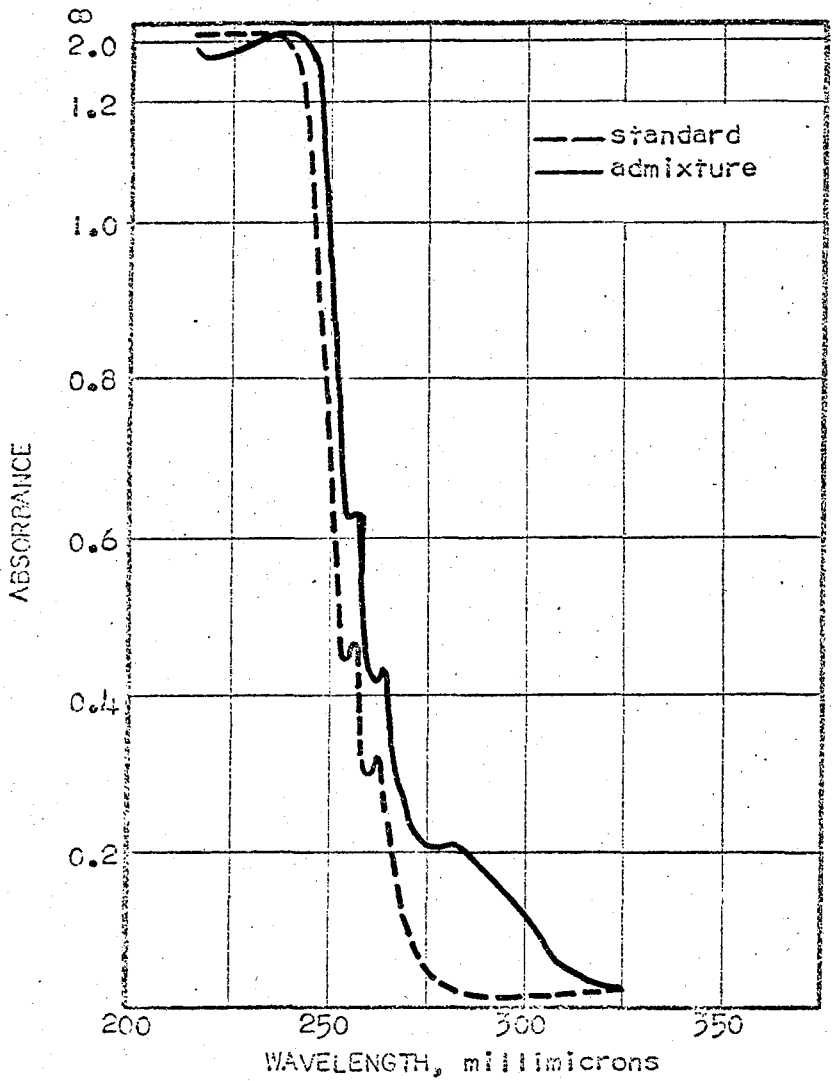
Change in pH of Tolazoline Hydrochloride-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Tolazoline Hydrochloride, 50mcg./ml. | 4.0 | 4.0 | 4.1 |
| Therapeutic Admixture | 3.8 | 3.7 | 3.7 |
| Dilution | 3.7 | 3.7 | 3.7 |

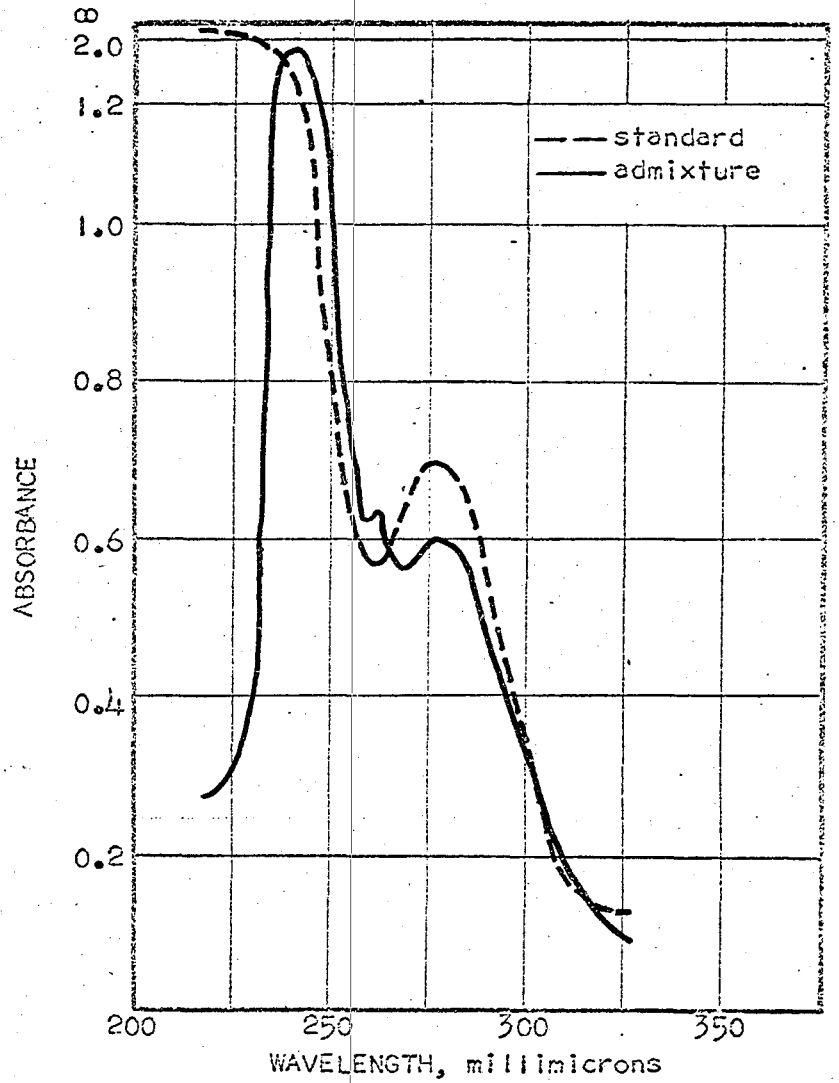



Graph 10

Standard Curve for Tolazoline Hydrochloride

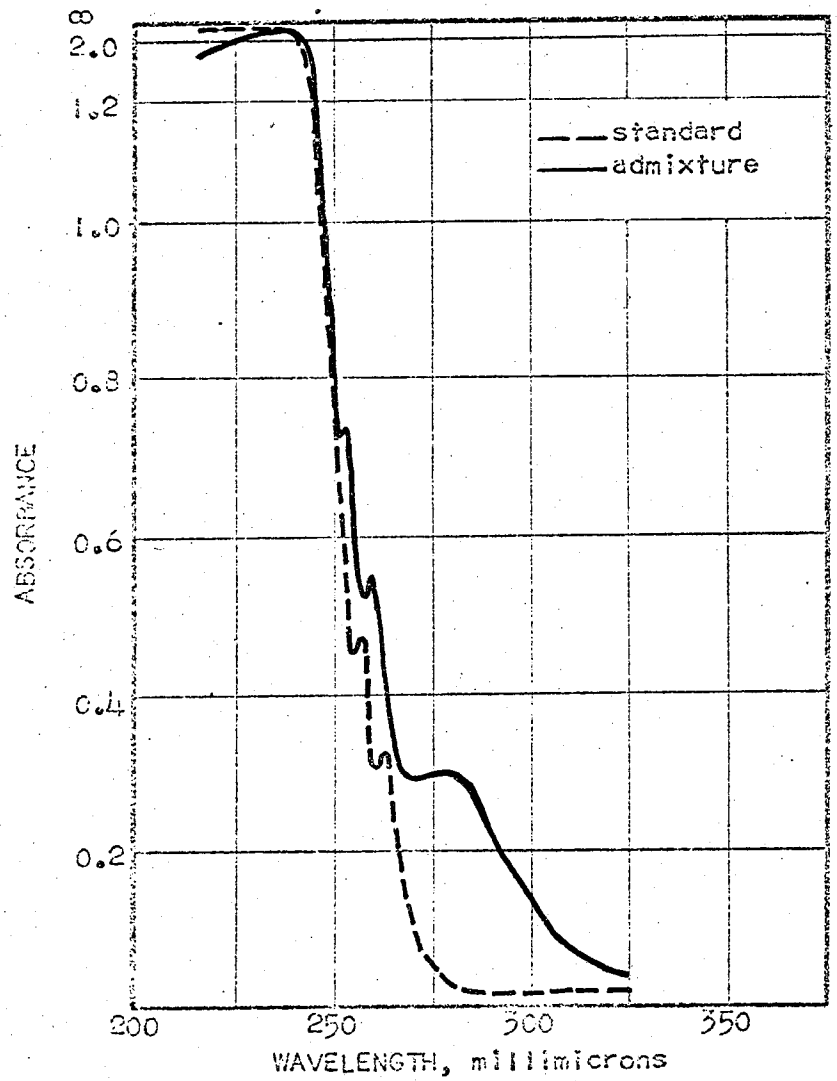



Tolazoline Hydrochloride, 400mcg./ml.
Ref. Sodium Ethacrynate, 50mcg./ml.

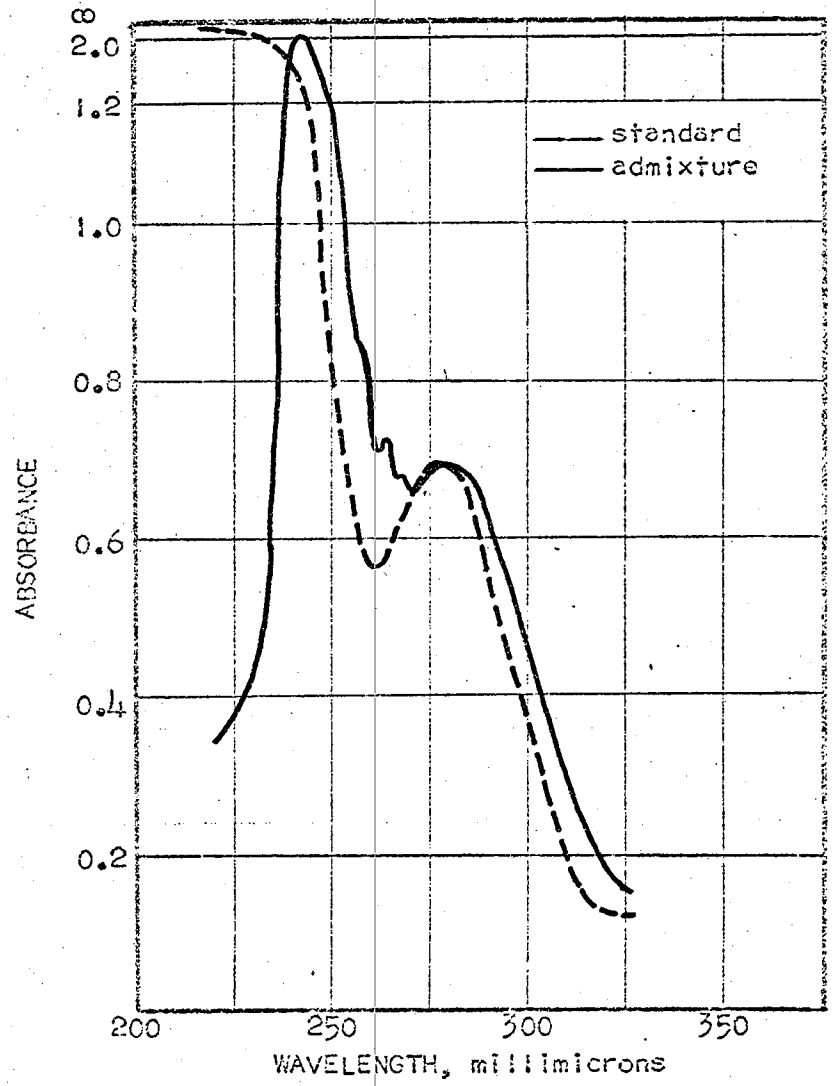



Sodium Ethacrynate, 50mcg./ml.
Ref. Tolazoline Hydrochloride, 400mcg./ml.

Fig. 22. U.V. Spectra of Admixture of Sodium Ethacrynate ($\lambda$ max 280) with Tolazoline Hydrochloride ($\lambda$ max 257) at 1 Hour.

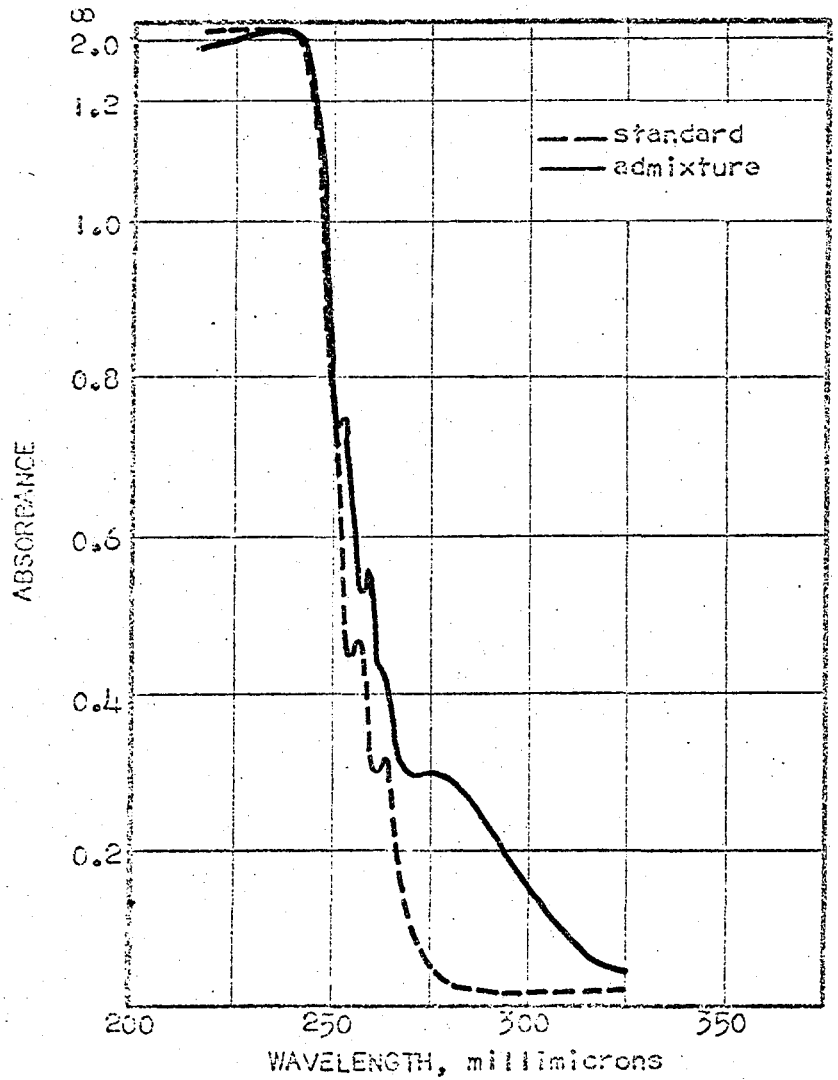



Tolazoline Hydrochloride, 400mcg./ml.
Ref. Sodium Ethacrynate, 50mcg./ml.

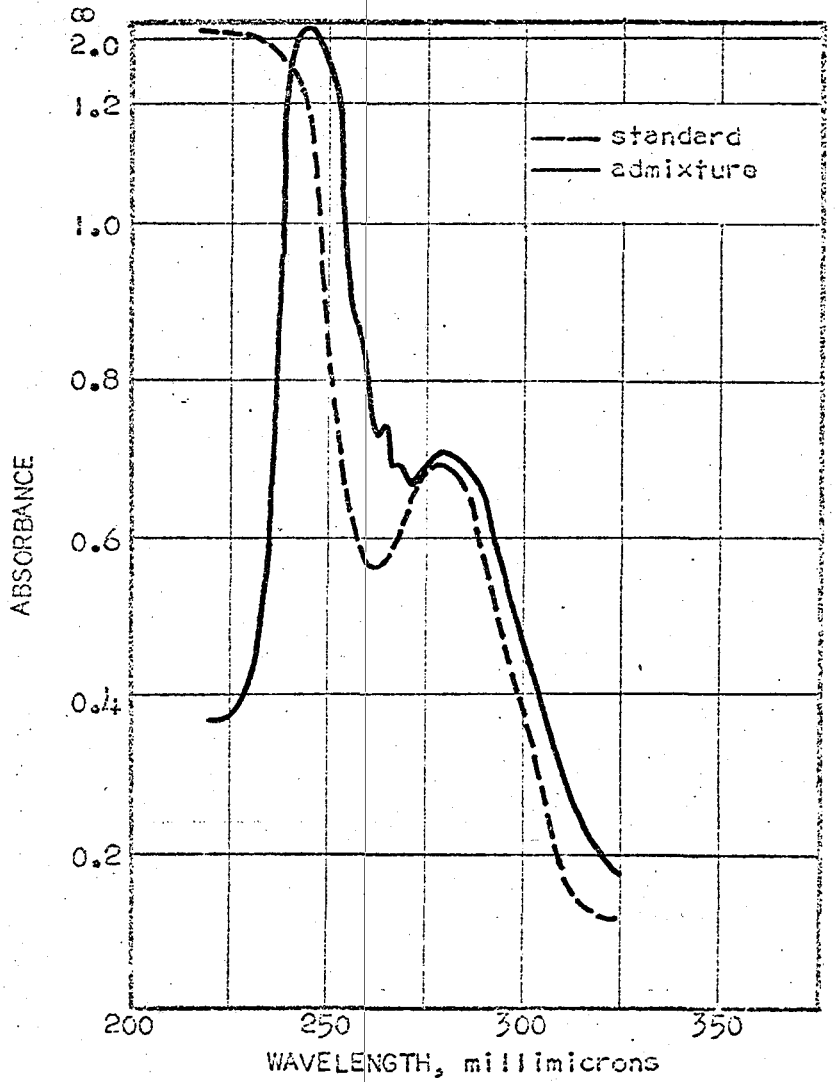



Sodium Ethacrynate, 50mcg./ml.
Ref. Tolazoline Hydrochloride, 400mcg./ml.

Fig. 23. U.V. Spectra of Admixture of Sodium Ethacrynate ($\lambda$ max 280) with Tolazoline Hydrochloride ($\lambda$ max 257) at 4 Hours.




Tolazoline Hydrochloride, 400mcg./ml.
Ref. Sodium Ethacrynate, 50mcg./ml.




Sodium Ethacrynate, 50mcg./ml.
Ref. Tolazoline Hydrochloride, 400mcg./ml.

Fig. 24. U.V. Spectra of Admixture of Sodium Ethacrynate ($\lambda$ max 280) with Tolazoline Hydrochloride ($\lambda$ max 257) at 8 Hours.

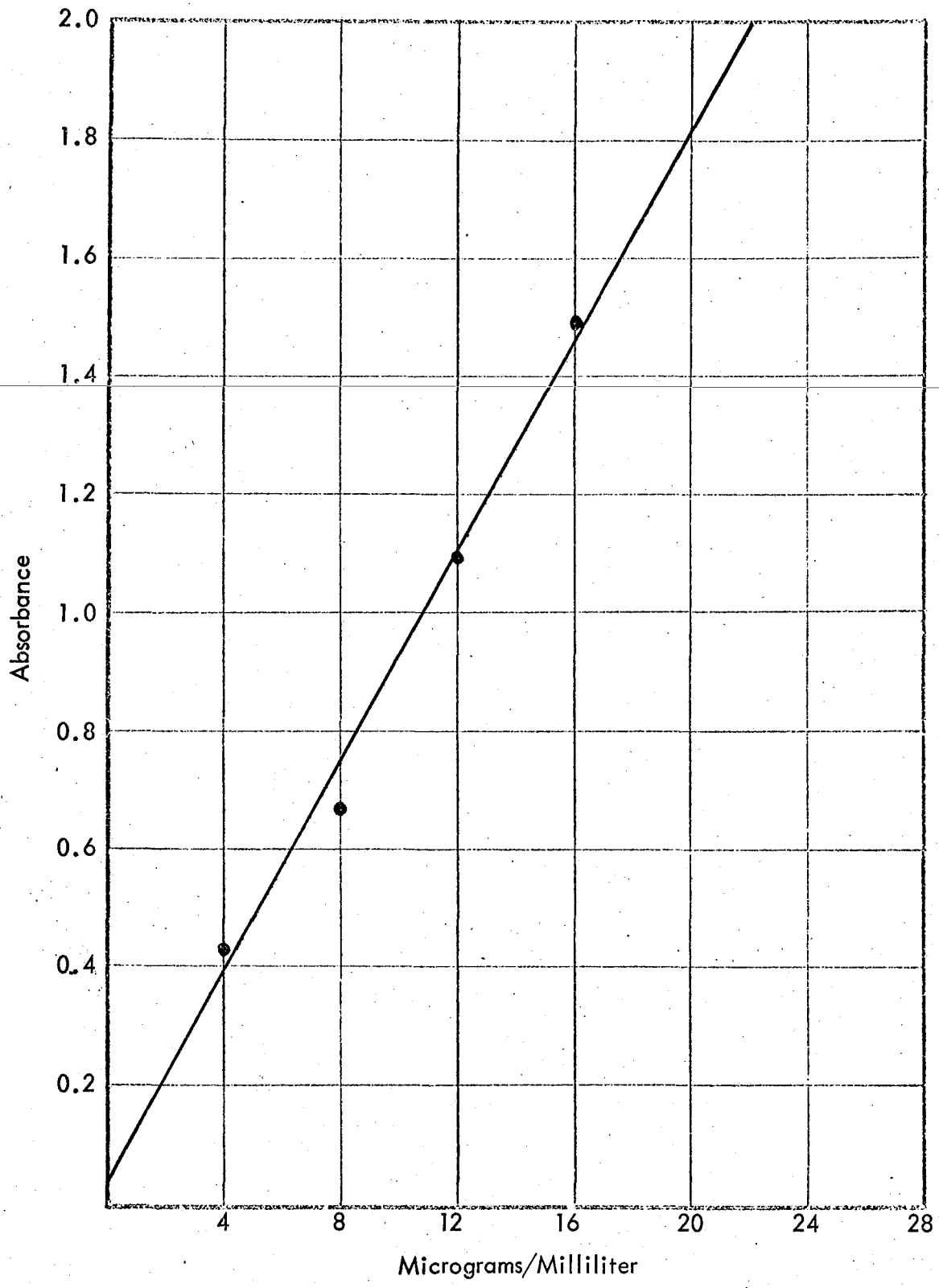
Trifluprom azine Hydrochloride-Sodium Ethacrynate

Admixtures of sodium ethacrynate and trifluprom azine hydrochloride, 50mcg./ml., and 5mcg./ml., respectively, caused the production of gas in the solution. This would indicate physical evidence of a chemical reaction, and prevented the use of spectrophotometric measurement of the admixture to determine any chemical interaction. Undiluted admixture of these two drugs resulted in a cloudy solution which also suggests a physical interaction. The results of the pH determinations are listed in Table X.

TABLE X

Change in pH of Trifluprom azine Hydrochloride-Sodium Ethacrynate Admixture During Eight Hour Period

| Solution | pH | | |
|---|---|---|---|
| | 1 Hour | 4 Hours | 8 Hours |
| Sodium Ethacrynate, 50mcg./ml. | 5.6 | 5.0 | 5.0 |
| Trifluprom azine Hydrochloride, 8mcg./ml. | 6.7 | 6.4 | 6.4 |
| Therapeutic Admixture | 5.2 | --- | --- |
| Dilution | 5.3 | --- | --- |




Graph 11

Standard Curve for Triflupromazine Hydrochloride

TABLE XI

RESULTS OF U.V. SPECTROPHOTOMETRIC EXAMINATION OF ADMIXTURE

| Admixture | Concentration (mcg./ml.) Therapeutic | Scanned[1] | Absorbance[2] | λmax[3] | Spectrum[4] |
|---|---|---|---|---|---|
| Sodium Ethacrynate | 50 | 40 | .55 | 280 | no change |
| Chlorpromazine HCl | 50 | 8 | .79 | 255 | no change |
| Sodium Ethacrynate | 50 | 50 | .7 | 280 | no change |
| Digitoxin | 0.2 | 20 | .41 | 222 | altered |
| Sodium Ethacrynate | 50 | 50 | .7 | 280 | no change |
| Digoxin | 1 | 40 | .79 | 220 | altered |
| Sodium Ethacrynate | 50 | 40 | .55 | 280 | altered |
| Hydralazine HCl | 20 | 16 | .87 | 241 | altered |
| Sodium Ethacrynate | 50 | 50 | .7 | 280 | altered |
| Procainamide HCl | 1000 | 8 | .51 | 280 | no change |
| Sodium Ethacrynate | 80 | 40 | .55 | 280 | no change |
| Prochlorperazine Ed. | 20 | 10 | .86 | 256 | no change |
| Sodium Ethacrynate | 50 | 40 | .55 | 280 | no change |
| Promazine HCl | 50 | 8 | .8 | 253 | no change |
| Sodium Ethacrynate | 50 | 50 | .7 | 280 | --- |
| Reserpine | 20 | 20 | .74 | 264 | --- |
| Sodium Ethacrynate | 50 | 50 | .7 | 280 | altered |
| Tolazoline HCl | 400 | 400 | .46 | 257 | altered |
| Sodium Ethacrynate | 50 | 50 | .7 | 280 | --- |
| Triflupromazine HCl | 5 | 5 | .45 | 256 | --- |

[1]Appropriate dilutions were performed using the solutions containing the parenteral products in therapeutic concentrations to achieve the values listed which are optimum concentrations.

[2]The absorbance values listed are the theoretical or standard values obtained by measuring each parenteral product alone in Sodium Chloride Injection, U.S.P.

[3]The λmax values listed are the theoretical or standard values obtained by measuring each parenteral product alone in Sodium Chloride Injection, U.S.P.

[4]The spectrum referred to is that measuring each parenteral product in admixture at the concentration listed. Two admixtures could not be measured spectrophotometrically due to the presence of a physical interaction.

TABLE XII

RESULTS OF VISUAL EXAMINATION OF ADMIXTURES

| Admixture[1] | Results | |
|---|---|---|
| | Undiluted[2] | Therapeutic[3] |
| Chlorpromazine HCl | Cloudy | Clear |
| Digitoxin | Clear | Clear |
| Digoxin | Clear | Clear |
| Hydralazine HCl | Clear | Clear |
| Procainamide HCl | Clear | Clear |
| Prochlorperazine Ed | Cloudy | Clear |
| Promazine HCl | Cloudy | Clear |
| Reserpine | Cloudy | Cloudy |
| Tolazoline HCl | Clear | Clear |
| Triflupromazine HCl | Cloudy | Evolution of Gas |

[1]Each parenteral product was mixed with Sodium Ethacrynate.

[2]Two drops of reconstituted Sodium Ethacrynate was mixed with two drops of each of the parenteral products on a microscope slide and examined immediately for physical evidence of an interaction.

[3]A therapeutic admixture of each parenteral product with Sodium Ethacrynate was made in Sodium Chloride Injection, U.S.P., and examined at one, four, and eight hours after preparation for physical evidence of an interaction. Any reactions that occurred were evident within one hour after the admixture was prepared.

# IV. DISCUSSION

Any method to detect chemical interactions of intravenous admixtures must consider several variables that may affect the results. As indicated earlier, the pH of the infusion fluid is of extreme importance. Acid-base reactions are the cause of a great number of incompatibilities of therapeutic agents in solution, and for this reason the pH stability range of a given drug must be considered when preparing admixtures of parenteral products.

The infusion vehicle can be considered to be an important determinant in the final pH of the solution. An examination of the acceptable pH ranges as recognized by the compendia show wide variance. In the case of Sodium Chloride Injection, U.S.P., a pH range of 4.5 to 7.0 is permissible (50). Because of this wide range, it is possible that a drug may be compatible in one lot of an infusion fluid but not in another. In the case of the sodium chloride injection used for this study, some variation in pH was noted. The pH range for this vehicle from a single lot of this infusion fluid was 5.1 to 6.8, which is within the allowable range.

Another factor that contributes to the pH of the admixture solution is the concentration and chemical nature of the additives. The effects of salts of strong acids and weak bases and salts of weak acids and strong bases are evident, and the concentration of these salts will, of course, affect the final pH. Agents that are present in small amounts have little effect upon the overall pH of the infusion fluid and, therefore, the possible pH related interaction

can be considered to be due to the vehicle itself.

The exposure of the parenteral products to atmospheric conditions greatly affects their pH. The dissolved gas content in the parenteral products is controlled until an admixture is prepared, or until the solution is used. Once the solution is exposed to oxygen and carbon dioxide, the pH of the solution can and will change.

For example, for a single Abbo-liter[a] container of sodium chloride injection, a change in pH from 6.8 to 6.2 was noted during an eight hour period. This infusion vehicle was exposed to the typical clinical procedure of removing portions of the solution using a Venopak Disposable Venoclysis Set #4622[a]. Although this may not have been a significant change in the pH, it may be of importance in assessing the results obtained. This is especially true in the case of drugs which have a narrow range of pH stability.

The concentration of the additives and the rate of the reaction are also of prime importance in assessing the results obtained from the experimental method. If the rate of the reaction is dependent upon the concentration of the additives, one must consider the effect of any dilutions that were performed. In the spectrophotometric procedure used, every effort was made to limit the admixture techniques to therapeutic concentrations. In certain instances the limitations of the spectrophotometer prevented this and appropriate dilutions were made in order to achieve optimum continuous absorbance spectra. It is possible that in diluting the admixture, some chemical interaction that might have occurred may have

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[a] Abbott Laboratories, North Chicago, Ill.

been eliminated if the reaction were concentration dependent.

The application of the method to actual hospital conditions is also an important factor in assessing the results of the study. It is desirable to have the method simulate the clinical situation. Every effort was made to duplicate the conditions found in a centralized intravenous additive program. Abbo-liter containers of the infusion solutions were used with Venopak Disposable Veno-clysis Sets to transfer the infusion fluids. Pipets of suitable size were used to prepare the various dilutions.

In obtaining the continuous U.V. absorption spectra for the admixtures, the need for using optimum concentrations cannot be overemphasized. This fact is quite important since the reference solution contained a parenteral product in sodium chloride injection. The effect of this was manifested by the occurrence of concentration dependent "noise" in the spectra obtained for certain admixtures. In spite of this, every effort was made to use therapeutic concentrations of each additive in order to simulate actual clinical conditions.

In assessing the data obtained, the results were discussed in terms of chemical interaction. A substantial decrease in the absorbance at the wavelength of maximum absorbance ( $\lambda$ max) would suggest a loss in concentration of the drug and, therefore, may be suggestive of a chemical interaction. An alteration in the continuous U.V. abosrption spectrum, such as the appearance of secondary peaks as compared to that of the spectrum of each parenteral product alone, would also suggest the presence of a chemical interaction.

Some mention must be made concerning the terminology used to describe

the various types of parenteral admixture interactions. As indicated in Chapter I, it has been suggested by several authors that the words "physical" and "chemical," when used to classify the types of incompatibilities, are a misnomer. This author is in agreement, for it is quite evident that any interaction involving two chemical entities is a "chemical interaction." A physical interaction (or incompatibility) is merely physical evidence of a chemical reaction.

Terminology has been suggested to replace the relatively meaningless words, "physical" and "chemical." These suggestions include "visual" and "non-visual" incompatibility, and also "soluble" and "insoluble" incompatibility. Indeed, it appears that the incompatibilities have been classified on the basis of the solubility of the end products of the reaction and not upon the types of reaction involved. If the reaction produces a visible change in the solution, it is considered to be a "physical" incompatibility. If a reaction occurs with no particulate matter produced, it is considered to be a "chemical" incompatibility. However, in actuality, the correct interpretation might be physical evidence or the lack of physical evidence of a chemical reaction.

# V. SUMMARY AND CONCLUSION

The purpose of this study was to devise a method of detecting chemical interactions of intravenous admixtures. Ultraviolet spectra of the drugs in combination were obtained. The spectra were examined for any loss in absorbance at the $\lambda$max, and also for any alteration in the spectra in the range of 200-325 millimicrons. Appreciable loss in absorbance at the $\lambda$max would suggest a loss in the concentration of the drug and therefore, would tend to indicate a chemical interaction. The appearance of a secondary $\lambda$max would be suggestive of an alteration in the chemical nature of the drug, and therefore, would also indicate a chemical interaction.

In the investigation of sodium ethacrynate in combination with the selected cardiovascular and psychotherapeutic agents, two parenteral products resulted in visible evidence of an interaction. Admixture with reserpine resulted in a cloudy solution, while in the admixture with trifluprομazine hydrochloride, the evolution of a gas was noted. These two admixtures demonstrate physical evidence of a chemical interaction.

The admixture of sodium ethacrynate with chlorpromazine hydrochloride, prochlorperazine edisylate, and promazine hydrochloride, gave no evidence of an interaction. The admixture of therapeutic concentration did not produce any physical evidence of an interaction. The spectrum for each drug in the admixture was not appreciably altered throughout the eight hour study.

Three admixtures with sodium ethacrynate exhibited a loss in absorbance

at the wavelength of maximum absorbance: digitoxin, digoxin, and procainamide hydrochloride. This loss may be considered to be suggestive of a decrease in the concentration of the additives.

A pronounced alteration in the spectra occurred with sodium ethacrynate when mixed with hydralazine hydrochloride and also with tolazoline hydrochloride. This change is indicative of a change in the chemical identity of the drug and is suggestive of a chemical interaction.

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